(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 226 304**
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 86308321.8

(22) Date of filing: 24.10.86

(51) Int. Cl.⁴: A61K 31/40 , A61K 31/43 , //(A61K31/40,31:195),(A61K31/-43,31:195)

(30) Priority: 24.10.85 JP 238283/85
10.04.86 JP 81218/86

(43) Date of publication of application:
24.06.87 Bulletin 87/26

(84) Designated Contracting States:
AT BE CH DE ES FR GB IT LI LU NL SE

(71) Applicant: SANKYO COMPANY LIMITED
No. 1-6, 3-chome Nihonbashi Honcho
Chuo-ku
Tokyo(JP)

(72) Inventor: Shiokari, Takashi c/o Product Development Labs.
Sankyo Co. Ltd. 2-58, 1-chome
Hiromachi Shinagawa-ku Tokyo(JP)
Inventor: Ueda, Seigo c/o Product Development Labs.
Sankyo Co. Ltd. 2-58, 1-chome
Hiromachi Shinagawa-ku Tokyo(JP)
Inventor: Iwata, Masayuki c/o Product Development Labs.
Sankyo Co. Ltd. 2-58, 1-chome
Hiromachi Shinagawa-ku Tokyo(JP)
Inventor: Kawahara, Yukinori c/o Product Development Labs.
Sankyo Co. Ltd. 2-58, 1-chome
Hiromachi Shinagawa-ku Tokyo(JP)

(74) Representative: Gibson, Christian John Robert et al
MARKS & CLERK 57/60 Lincoln's Inn Fields
London WC2A 3LS(GB)

(54) Composition containing a penem or carbapenem antibiotic and the use of the same.

(57) Administration of an N-acylated amino acid in association with a penem or carbapenem antibiotic relieves or eliminates the renal problems associated with administration of the antibiotic alone. The amino acid derivative and antibiotic may be formulated together as a composition or administered separately, either simultaneously or sequentially. The composition may be prepared by simple mixing.

EP 0 226 304 A1

COMPOSITION CONTAINING A PENEM OR CARBAPENEM ANTIBIOTIC AND THE USE OF THE SAME

The present invention relates to a novel composition comprising a penem or carbapenem antibiotic in association with an amino acid derivative. The invention also provides a method of treating bacterial infections by administering to the patient, simultaneously or sequentially, a penem or carbapenem antibiotic and at least one N-acylated amino acid.

The class of compounds known as "penem and carbapenem antibiotics" is, of course, very well known and is potentially of great value for the treatment of bacterial infections. Although, as a group, these penem and carbapenem antibiotics exhibit excellent anti-bacterial activity and a variety of other properties which render them highly suitable for pharmaceutical use, they do have a number of disadvantages. One of the problems of these antibiotics is that, in general, they exhibit a degree of renal toxicity, and some degree of kidney damage is a frequent side effect of their use; accordingly, such penem and carbapenem antibiotics should not be used for the treatment of patients with actual or suspected impaired renal function. As a result, the penem and carbapenem antibiotics cannot be used for many patients for whom otherwise they would be the antibiotic of choice. The problem of renal toxicity is particularly acute when the antibiotics are administered by intravenous or intramuscular injection in a high dose.

We have now surprisingly discovered that the concurrent, or effectively concurrent, administration, with the penem or carbapenem antibiotic, of one or more of a certain class of acylated amino acid derivatives significantly reduces this renal toxicity.

EP Publication No. 7614 discloses the use of a dipeptidase inhibitor in associated with antibiotics similar to those to which the present invention relates. However, the dipeptidase inhibitors employed are structurally different from the amino acid derivatives of the present invention and are employed for a totally different purpose. The amino acid derivatives of the present invention and are employed for a totally different purpose. The amino acid derivatives employed in the present invention possess little or no dipeptidase inhibitory activity.

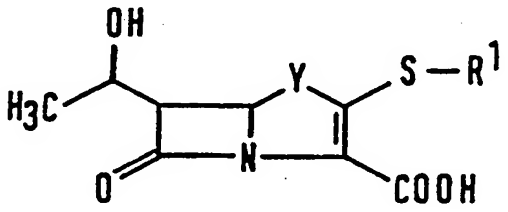
Accordingly, in one aspect, the present invention provides a composition comprising:

(a) a penem or carbapenem antibiotic; and

(b) a pharmaceutically acceptable N-acrylated derivative of an amino acid wherein the amino group and the carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof, provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.

EP Application No. 85307427.6 discloses such a composition where the amino acid is ornithine, lysine, phenylalanine or phenylglycine.

There is no particular limitation on the nature of the penem or carbapenem antibiotic to which the present iinvention can be applied and it is believed that the beneficial effects of the concurrent administration of the N-acylated amino acid derivative will be achieved regardless of the particular antibiotic chosen. However, the penem and carbapenem antibiotics which are currently of most actual or potential interest may be represented by the general formula (I):



(I)

in which:

Y represents a sulphur atom, a methylene group or a methylene group having 1 or 2 methyl and/or methoxy substituents; and

R¹ represents a C_1-C_6 alkyl group, a C_1-C_6 alkyl group having at least one of substituents (i) or a heterocyclic group having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms where said heterocyclic group is unsubstituted or has at least one of substituents (ii);

substituents (i):

halogen atoms, amino groups, amino groups having at least one of substituents (iii), C_1-C_4 alkylideneamino

groups, C_1-C_4 aminoalkylideneamino groups, amidino groups, amidino groups having from 1 to 3 of substituents (iii), heterocyclic groups having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms wherein said heterocyclic group is unsubstituted or has at least one of substituents (ii), imino groups, cyano groups, carbamoyl groups and carbamoyl groups having at least one C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituent;

substituents (ii):

C_1-C_6 alkanimidoyl groups, C_1-C_6 alkyl groups, alkoxyalkyl groups where the alkoxy and alkyl parts are each C_1-C_4, carbamoyl groups, carbamoyl groups having at least one C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituent, C_1-C_4 haloalkyl groups, heterocyclic acylimidoyl groups where the heterocyclic part has from 5 to 9 ring atoms of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms, amidino groups, amidino groups having from 1 to 3 of substituents (iii), imino groups, oxygen atoms, C_1-C_6 alkanoyl groups, C_1-C_6 alkanesulphonyl groups, C_1-C_6 alkanesulphinyl groups, hydroximino groups, C_1-C_4 alkoximino groups, carbamoyloxy groups, carbamoyloxy groups having at least one C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituent, carbamoyloxyalkyl groups where the alkyl part is C_1-C_4 and the carbamoyl part is unsubstituted or has at least one C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituent and C_1-C_4 iminoalkyl groups;

substituents (iii):

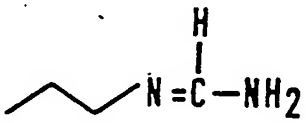
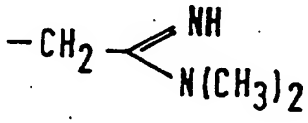
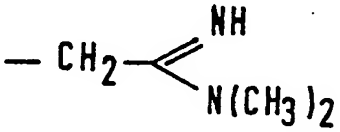
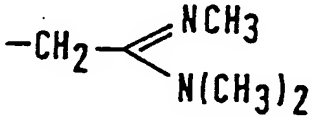
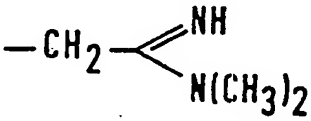
C_1-C_6 alkyl groups, C_2-C_6 alkenyl groups, C_2-C_6 alkynyl groups, oxygen atoms and said alkyl, alkenyl and alkynyl groups having at least one substituent selected from halogen atoms, carbamoyloxy groups and carbamoyloxy groups having at least one C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituent.

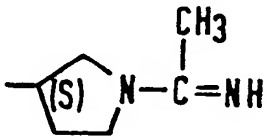
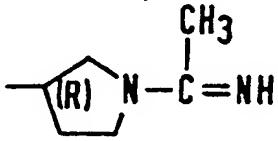
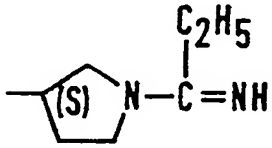
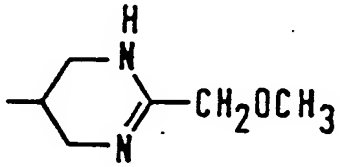
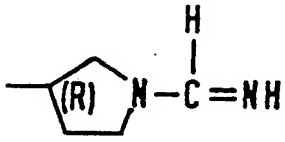
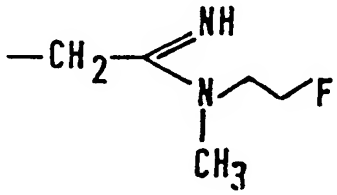
Preferably Y represents a sulphur atom, a methylene group, or the group CH_3-CH<, CH_3O-CH< or -$(CH_3)_2C$<.

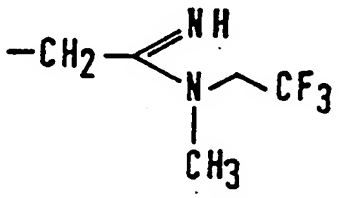
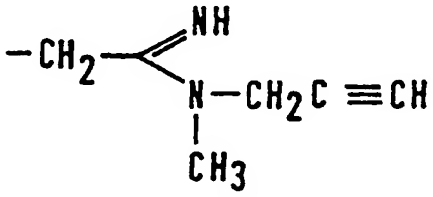
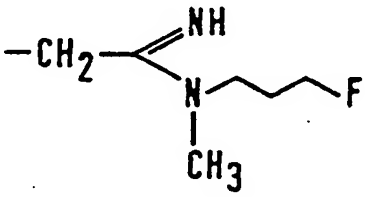
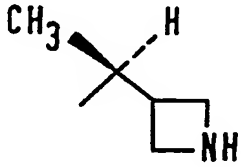
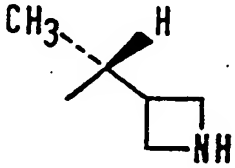
Preferred examples of groups which may be represents by R' include the ethyl, 2-fluoroethyl, 2-(aminomethyleneamino(ethyl, N',N'-dimethylamidinomethyl, N',N',N²-trimethylamidinomethyl, 3-pyrrolidinyl, 1-formimidoyl-3-pyrrolidinyl, 1-acetimidoyl-3-pyrrolidinyl, 1-propionimidoyl-3-pyrrolidinyl, 2-methyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 2-methoxymethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 3-azetidinyl, 1-acetimidoyl-3-azetidinyl, N'-methyl-N'-(2-propynyl)amidinomethyl, N'-(2-fluoroethyl)-N'-methylamidinomethyl, N'-(3-fluoropropyl)-N'-methylamidinomethyl, N'-methyl-N'-(2,2,2-trifluoroethyl)amidinomethyl, 1-(3-azetidinyl)ethyl, 1-(1-acetimidoyl-3-azetidinyl)ethyl, 1,4,5,6-tetrahydro-2-pyrimidinylmethyl, 1-(4,5-dihydro-2-thiazolyl)ethyl, 5-carbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-carbamoyl-3-pyrrolidinyl, 2-chloromethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 1-butyrimidoyl-3-pyrrolidinyl, 1-nicotinimodyl-3-pyrrolidinyl, N',N'-diallylamidinomethyl, N'-methyl-N'-(2-propynyl)amidino, N'-(2-fluoroethyl)-N'-methylamidino, N'-(3-fluoropropyl)-N'-methylamidino, N'-methyl-N'-(2,2,2-trifluoroethyl)amidino, N'-allyl-N'-methylamidinomethyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 2-cyano-1-methylethyl, 2-aminoethyl, 1-carbamoylethyl, 2-(1-aminoethylideneamino)ethyl, 1-amidino-3-pyrrolidinyl, 2-methyl-1,3-diazabicyclo[3.3.0]oct-2-en-7-yl, 2-methoxymethyl-1,3-diazabicyclo-[3.3.0]oct-2-en-7-yl, 5-imino-2-pyrrolidinyl, 2-imino-5-piperidinyl, 1-acetimidoyl-5-methylcarbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-methoxycarbamoyl-3-pyrrolidinyl, 2-imino-2-(S-oxothiomorpholino)ethyl, 2-imino-2-(1,1-dioxo-1,3-thiazolidin-3-yl)ethyl, 2-imino-2-(S,S-dioxothiomorpholino)ethyl, 2-imino-2-(3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-acetyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methanesulphonyl-3-oxo-1-piperazinyl)ethyl, N'-(2-carbamoyloxyethyl)-N'-methylamidinomethyl, 2-(3-hydroximino-1-pyrrolidinyl)-2-iminoethyl, 2-imino-2-(3-methoximino-1-pyrrolidinyl)ethyl, 2-(4-hydroximinopiperidino)-2-iminoethyl, 2-imino-2-(4-methoximinopiperidino)ethyl, 2-(3-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-imino-2-(3-oxo-1-piperazinyl)ethyl, 2-(3-carbamoylpiperidino)-2-iminoethyl, 2-(3-carbamoyloxypiperidino)-2-iminoethyl, 2-(2-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-(2-carbamoyloxymethyl-1-pyrrolidinyl)-2-iminoethyl, 2-(4-carbamoyloxypiperidino)-2-iminoethyl, 2-(4-formyl-1-piperazinyl)-2-iminoethyl, 2-(4-acetyl-1-piperazinyl)-2-iminoethyl, 1-formyl-3-azetidinyl, 1-iminomethyl-3-azetidinyl, 1-methyl-4-piperidyl, 1-acetimidoyl-4-piperidyl and 1-acetyl-3-pyrrolidinyl groups.

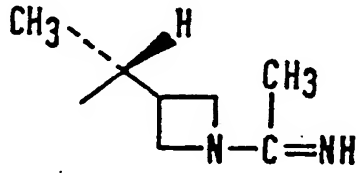
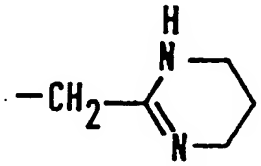
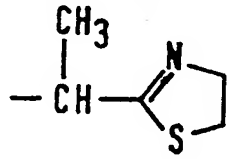
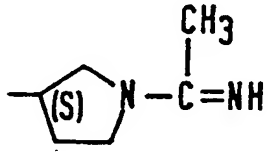
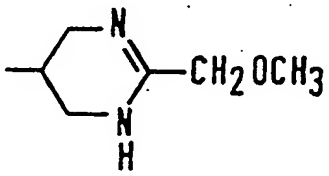
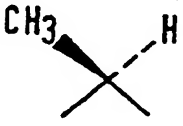
The invention may also be applied to pharmaceutically acceptable salts and esters of such antibiotics, such as are well known in the art.

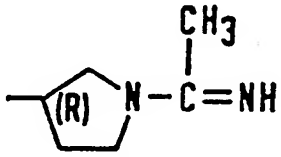
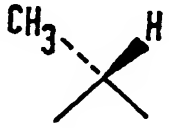
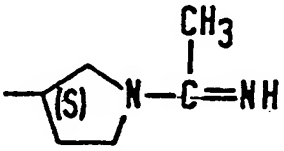
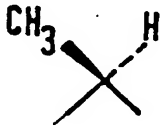
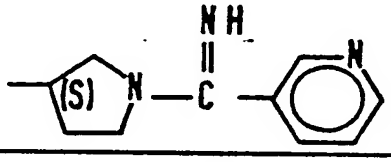
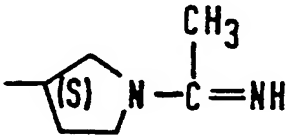
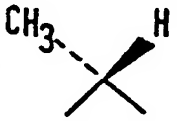
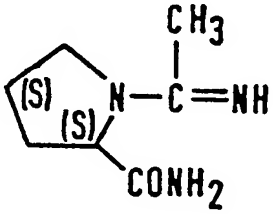
Specific examples of compounds of formula (I) which may be employed in the present invention are those in which R' and Y are as defined below:

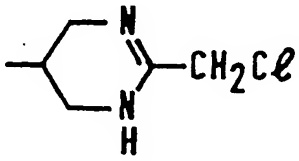
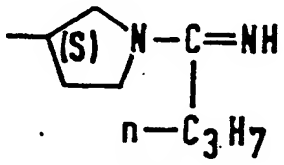
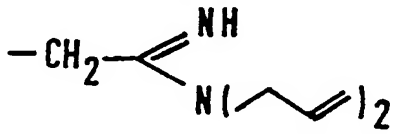
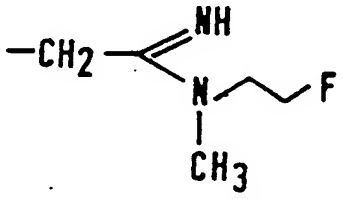
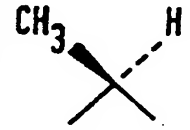
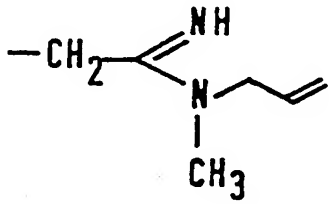
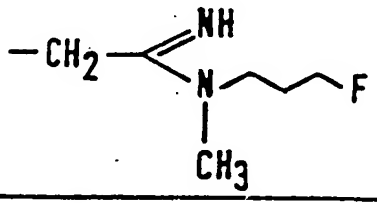
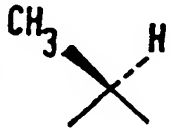
Comp. No.	R1	Y
1.		CH_2
2.		CH_2
3.		
4.		CH_2
5.		S

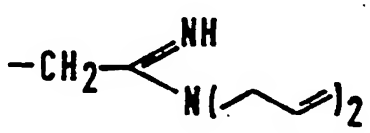
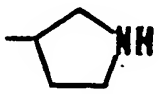
Comp. No.	R^1	Y
6.		CH_2
7.		CH_2
8.		CH_2
9		CH_2
10.		CH_2
11.		CH_2

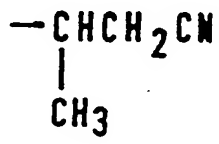
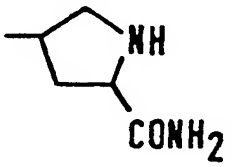
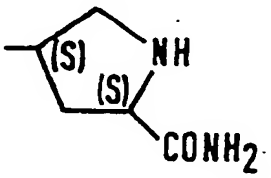
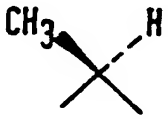
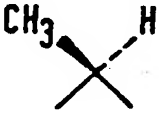
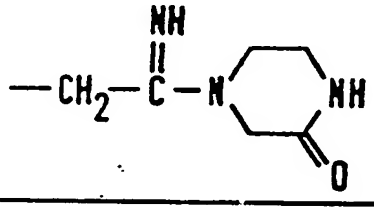
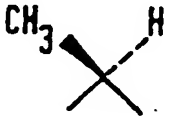
Comp. No.	R^1	Y
12.		CH_2
13.		CH_2
14.		CH_2
15.		CH_2
16.		CH_2

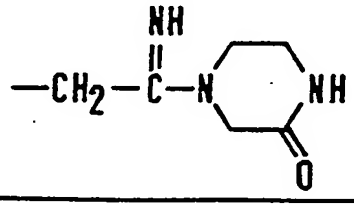
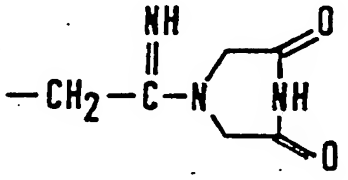
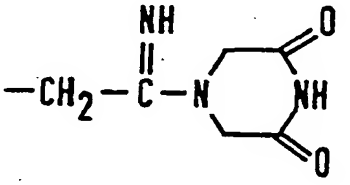
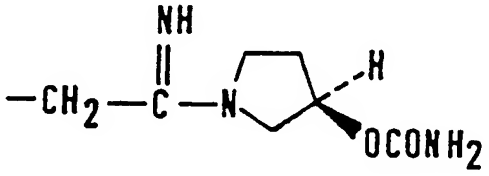
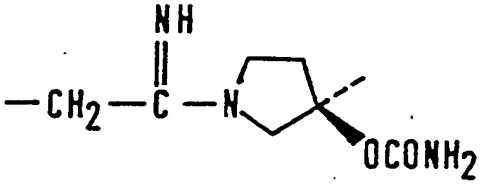
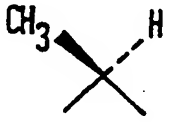
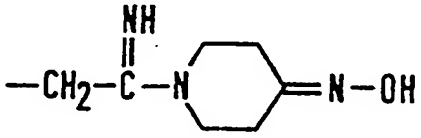
Comp. No.	R^1	Y
17.		CH_2
18.		CH_2
19.		CH_2
20.		
21.		
22.		

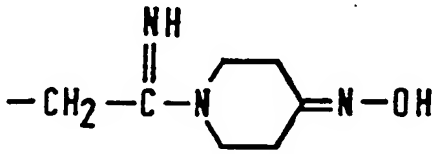
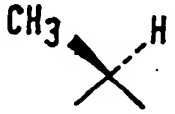
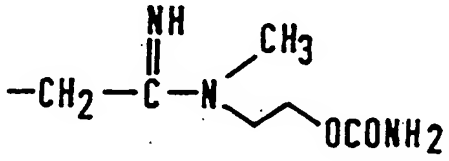
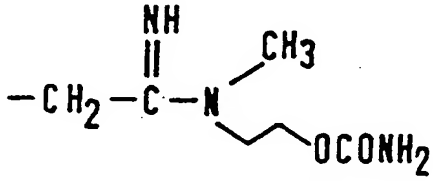
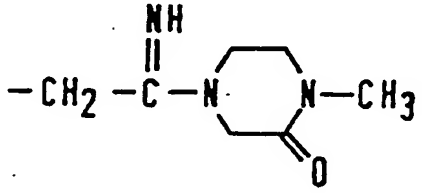
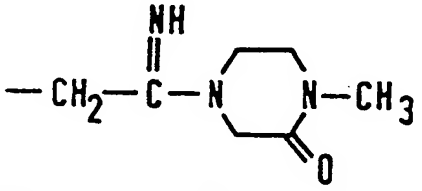
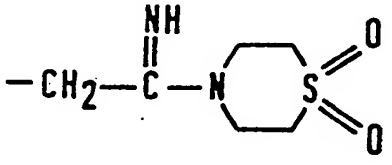
Comp. No.	R^1	Y
23.		
24.		
25.		
26.		CH_2
27.		
28.		CH_2

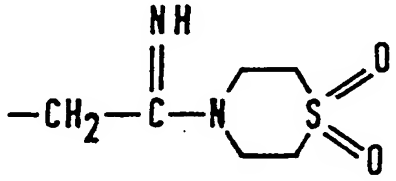
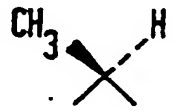
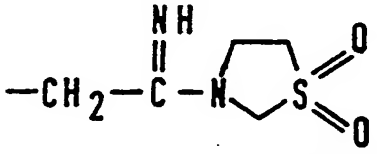
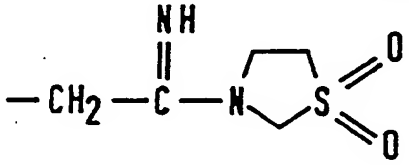
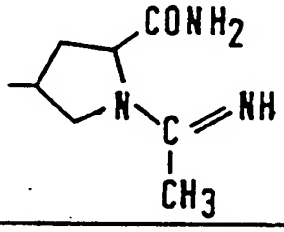
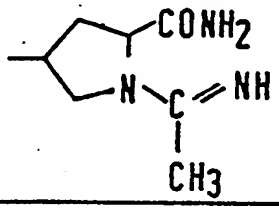
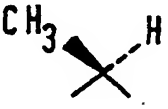
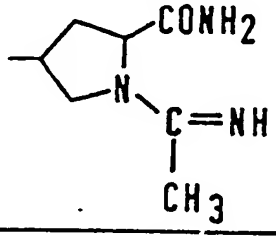
Comp. No.	R^1	Y
29.		CH_2
30.		CH_2
31.		CH_2
32.		
33.		
34.		

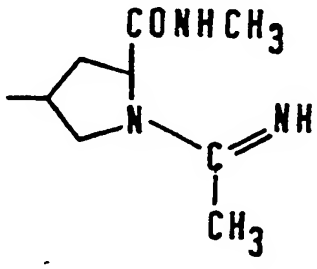
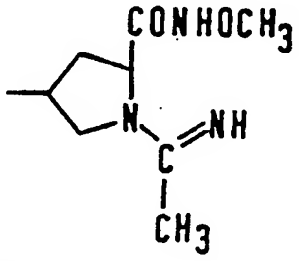
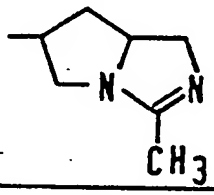
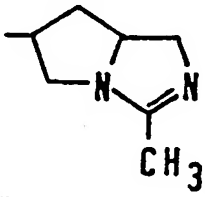
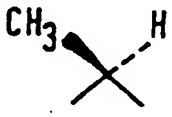
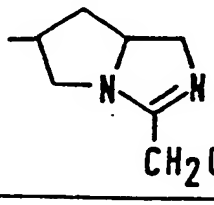
Comp. No.	R^1	Y
35.		
36.	$-CH_2CH_3$	S
37.	$-CH_2CH_2F$	S
38.		S
39.	$-CH_2CN$	S
40.	$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}CN$	S
41.	$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}CONH_2$	S
42.	$-CH_2CH_2NH_2$	S
43.	$\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}CH_2CN$	CH_2

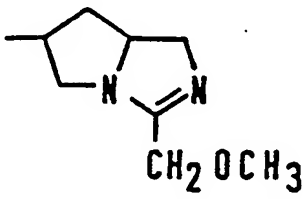
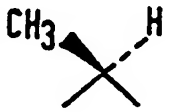
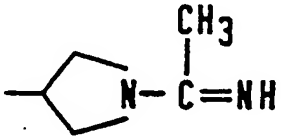
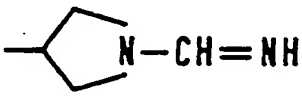
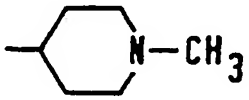
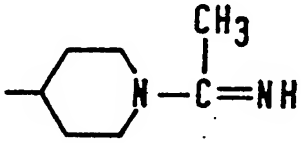
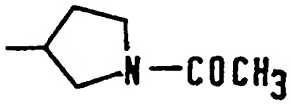
Comp. No.	R^1	Y
44.		S
45.		CH_2
46.		CH_2
47.		CH_2
48.		
49.		
50.		

Comp. No.	R^1	Y
51.		CH_2
52.		CH_2
53.		
54.		CH_2
55.		
56.		CH_2

Comp. No.	R^1	Y
57.		
58.		CH_2
59.		
60.		CH_2
61.		
62.		CH_2

Comp. No.	R^1	Y
63.		
64.		CH_2
65.		
66.		CH_2
67.		
68.		

Comp. No.	R^1	Y
69.		CH_2
70.		CH_2
71.		CH_2
72.		
73.		CH_2

Comp. No.	R^1	Y
74.		
75.		CH_2
76.		CH_2
77.		CH_2
78.		CH_2
79.		CH_2

Of the compounds listed above, we particularly prefer those which have the same configuration as thienamycin, i.e. (5R,6S)-6-[1(R)-hydroxyethyl]. In particular, the following compounds are preferred:
(5R,6S)-2-{2-[(aminomethylene)amino]ethylthio}-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid - (isomer of Compound No. 1)
(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid - (isomer of Compound No. 6)
(5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid - (isomer of Compound No. 7)
(5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S)-methyl-2-carbapenem-3-carboxylic acid (isomer of Compound No. 23)
(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(R)-methyl-2-carbapenem-3-carboxylic acid (isomer of Compound No. 24)

(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S)-methyl-2-carbapenem-3-carboxylic acid (isomer of Compound No. 27)

(5R,6S)-2-[(3S)-1-acetimidoyl-5(S)-carbamoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid (isomer of Compound No. 28)

The above compounds may likewise be employed in the form of their pharmaceutically acceptable salts or esters, examples of which are well-known to those skilled in the art and which are given, for example, in US Patent No. 4,552,873.

The protective effect against renal toxicity appears to be exhibited by the whole range of amino acids wherein the amino and carboxylic acid groups are attached to a saturated aliphatic carbon chain or carbon atom. However, we have found that best results are achieved when employing N-acylated derivatives of those amino acids which may be represented by the formula (II):

H_2N-X-COOH (II)

wherein X represents a C_1-C_{10} alkylene group or a C_1-C_{10} alkylene group having at least one substituent selected from hydroxy groups, C_1-C_4 alkoxy groups, C_6-C_{14} aryloxy groups, substituted C_6-C_{14} aryloxy groups, C_7-C_9 aralkyloxy groups, substituted C_7-C_9 aralkyloxy groups, mercapto groups, C_1-C_4 alkylthio groups, C_6-C_{14} arylthio groups, substituted C_6-C_{14} arylthio groups, C_7-C_9 aralkylthio groups, substituted C_7-C_9 aralkylthio groups, C_2-C_5 carboxyalkylthio groups, amino groups, amino groups having one or two substituents selected from

C_1-C_4 alkyl groups, C_6-C_{14} aryl groups, substituted C_6-C_{14} aryl groups, C_7-C_9 aralkyl groups, substituted C_7-C_9 aralkyl groups and carboxylic acyl groups,

C_6-C_{14} aryl groups, substituted C_6-C_{14} aryl groups, carboxy groups, amidino groups, sulpho groups, C_1-C_4 alkylsulphinyl groups, C_1-C_4 alkylsulphonyl groups and heterocyclic groups having from 5 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said substituted aryloxy, aralkyloxy, arylthio, aralkylthio, aryl and aralkyl groups having at least one substituent selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups.

In general terms, the N-acylated derivatives of these amino acids may be represented by the formula - (III):

R^2HN-X-COOH (III)

wherein R^2 represents a carboxylic acyl group and X is as defined above.

Examples of carboxylic acyl groups which may be represented by R^2 include:

alkanoyl groups, and preferably alkanoyl groups having from 1 to 18, more preferably from 1 to 10 and still more preferably from 1 to 8, e.g. from 2 to 5 or from 5 to 8, carbon atoms, for example the acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, nonanoyl and decanoyl groups; in the case of those amino acids which have relatively bulky and lipophilic groups, lower - (e.g. C_2-C_5) alkanoyl groups are preferred; for others (e.g. glycine), higher (e.g. C_6-C_8) groups are preferred;

alkenoyl and alkynoyl groups, and more preferably such groups having from 3 to 8, more preferably 3 or 4, carbon atoms, for example the acryloyl, methacryloyl, crotonoyl or propioloyl groups;

aromatic acyl groups in which the aryl ring is a carbocyclic ring having from 6 to 14, preferably 6 to 10, carbon atoms and optionally having from 1 to 5, more preferably from 1 to 3, substituents preferably selected from C_1-C_4 alkyl groups, hydroxy groups, C_1-C_4 alkoxy groups, amino groups, sulpho groups and halogen atoms, for example the benzoyl and naphthoyl (1-or 2-naphthoyl) groups and the benzoyl and naphthoyl (1-or 2-naphthoyl) groups having one or more of the above substituents, for example the p-toluoyl, m-toluoyl, o-toluoyl, 4-butylbenzoyl, 4-hydroxybenzoyl, 3-hydroxybenzoyl, 2-hydroxybenzoyl, 4-methoxybenzoyl, 3-methoxybenzoyl, 2-methoxybenzoyl, 4-butoxybenzoyl, 4-aminobenzoyl, 3-aminobenzoyl, 2-aminobenzoyl, 3-sulphobenzoyl, 4-chlorobenzoyl, 3-fluorobenzoyl, 2-bromobenzoyl, 3-hydroxy-2-naphthoyl and 1-hydroxy-2-naphthoyl groups;

alicyclic acyl groups in which the carbocyclic ring has unsubstituted or has at least one C_1-C_4 alkyl and/or phenyl substituent, for example the cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, 1-phenyl-1-cyclopropanecarbonyl, 1-phenyl-1-cyclopentanecarbonyl, 1-methyl-1-cyclohexanecarbonyl and 1-phenyl-1-cyclohexanecarbonyl groups;

araliphatic acyl groups in which the aryl ring is a carbocyclic ring having from 6 to 14, preferably 6 to 10, carbon atoms and optionally having from 1 to 5, more preferably from 1 to 3, substituents preferably selected from C_1-C_4 alkyl groups, hydroxy groups, C_1-C_4 alkoxy groups, amino groups, sulpho groups and halogen atoms, and in which the alkyl moiety has from 1 to 4 carbon atoms, such as the phenylacetyl, α-phenyl-α-methylacetyl, α-phenyl-α-ethylacetyl, α,α-diphenylacetyl, α-phenyl-α-cyclopentyl-acetyl, 3-phenylpropionyl, 4-phenylbutyryl, 4-tolylacetyl, 4-hydroxyphenylacetyl, 4-aminophenylacetyl, 4-methoxyphenylacetyl, 3-sulphophenylacetyl and 4-chlorophenylacetyl groups;

heterocyclic acyl groups which may have saturated or unsaturated ring systems, the rings having 5 or 6

ring atoms, of which from 1 to 3 are nitrogen and/or sulphur and/or oxygen hetero-atoms and the ring being unsubstituted or having from 1 to 3 C_1-C_4 alkyl and/or hydroxy substituents, for example the nicotinoyl, 2-thiophenecarbonyl, 2-furoyl, 2-pyrazinecarbonyl, 2-piperidinecarbonyl, N-methylnicotinoyl and 6-hydroxynicotinoyl groups;

alkoxycarbonyl groups having a total of from 2 to 7 carbon atoms, for example the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl and pentyloxycarbonyl groups; and

aralkyloxycarbonyl groups in which the aralkyl moiety has from 7 to 9 carbon atoms and is unsubstituted or has from 1 to 5, more preferably from 1 to 3, substituents selected from amino groups, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups and hydroxy groups, for example the benzyloxycarbonyl, α-methylbenzyloxycarbonyl, phenethyloxycarbonyl, 3-phenylpropoxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-hydroxybenzyloxycarbonyl, p-tolyloxycarbonyl and 4-aminobenzyloxycarbonyl groups.

In addition to the acyl groups listed above, R^2 can also represent an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups. Hence, R^2 can also represent such an acyl group connected to the parent amino acid via one or more amino acid residues, preferably from 0 to 5, more preferably from 0 to 3 and most preferably from 0 to 2, such residues. Thus, R^2 could represent a group derived from an N-acylated amino acid, for example the N-benzoylglycyl or N-benzoylglycylglycyl group. Hence, compounds of formula (I) also include such oligopeptide compounds as N-benzoylglycylglycine, N -benzoylglycylglycylglycine and similar compounds.

Preferred examples of groups which may be represented by R^2 include: saturated aliphatic acyl groups having from 1 to 8 carbon atoms; aromatic acyl groups in which the aryl moiety has from 6 to 10 ring carbon atoms and is unsubstituted or has from 1 to 3 C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituents; alicyclic acyl groups in which the cycloalkane ring has from 3 to 6 carbon atoms; araliphatic acyl groups in which the aryl ring has from 6 to 10 ring carbon atoms and the alkyl group has from 1 to 4 carbon atoms, the aryl ring being unsubstituted or having from 1 to 3 C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituents; heterocyclic acyl groups in which the heterocyclic ring is saturated or unsaturated and has 5 or 6 ring atoms of which one is a nitrogen, sulphur or oxygen hetero-atom; alkoxycarbonyl groups having a total of from 2 to 7 carbon atoms; and aralkyloxycarbonyl groups in which the aralkyl moiety has from 7 to 9 carbon atoms and the aryl ring is unsubstituted or has from 1 to 3 C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituents.

Particularly preferred groups which may be represented by R^2 include: aromatic acyl groups in which the aryl ring has from 6 to 10 ring atoms and which is unsubstituted or has a single substituent selected from C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups, hydroxy groups and amino groups; alicyclic acyl groups in which the cycloalkane moiety has from 3 to 6 carbon atoms; phenylaliphatic acyl groups in which the phenyl group is unsubstituted or has a single C_1-C_4 alkyl substituent, and in which the alkyl part has from 1 to 4 carbon atoms; alkoxycarbonyl groups having a total of from 4 to 6 carbon atoms; and aralkyloxycarbonyl groups in which the aralkyl part has from 7 to 9 carbon atoms and has 0 or 1 C_1-C_4 alkyl or C_1-C_4 alkoxy substituent.

In addition, such acyl groups linked to the amino acid via at least one further amino acid residue are preferred.

Of the groups exemplified above, the following are most preferred: acetyl, benzoyl, cyclohexanecarbonyl, cyclopropanecarbonyl, hexanoyl, isobutyryl, crotonoyl, ethoxycarbonyl, 4-hydroxybenzoyl, anisoyl, 4-aminobenzoyl, naphthoyl, toluoyl, benzyloxycarbonyl and 4-methoxybenzyloxycarbonyl groups, of which the acetyl and benzoyl, particularly benzoyl, groups are most preferred. As explained previously, the lower alkanoyl groups, notably the acetyl group, are only most preferred in relation to their use with those amino acids which have relatively bulky and lipophilic groups.

In the compounds of formula (II), X represents an alkylene group having from 1 to 10, preferably from 1 to 8 and more preferably from 1 to 5, carbon atoms. Such groups may have the "free" valencies attached to different carbon atoms or to the same carbon atom. In the latter case, the groups are sometimes referred to as "alkylidene" groups. Examples include the methylene, ethylidene, ethylene, propylidene, 1-methylethylidene, 1-methylethylene, trimethylene, butylidene, 2-methylpropylidene, 1-methylpropylidene, 1,2-dimethylethylene, 1-ethylethylene, 1-methyltrimethylene, 2-methyltrimethylene, tetramethylene, pentylidene, 3-methylbutylidene, 2-methylbutylidene, 2,2-dimethylpropylidene, 1-ethylpropylidene, 1,2-dimethylpropylidene, 1-propylethylene, 1-(1-methylethyl)ethylene, 1-ethyl-2-methylethylene, 1-ethyltrimethylene, 2-ethyltrimethylene, 1,3-dimethyltrimethylene, 1-methyltetramethylene, 2-methyltetramethylene, pentamethylene, hexylidene, 4-methylpentylidene, 3-methylpentylidene, 2-methylpentylidene, 1-methylpentylidene, 2-ethylbutylidene, 1-ethylbutylidene, 1,3-dimethylbutylidene, 1,2-dimethylbutylidene, 3,3-dimethylbutylidene, 2,3-dimethylbutylidene, 1-butylethylene, 1-methyl-2-propylethylene, 1,2-diethylethylene, 1-

methyl-1-propylethylene, 2-propyltrimethylene, 1-ethyl-3-methyltrimethylene, 1-ethyltetramethylene, 2-ethyltetramethylene, 1,3-dimethyltetramethylene, 1-methylpentamethylene, 2-methylpentamethylene, 3-methylpentamethylene, hexamethylene, heptylidene, 5-methylhexylidene, 4-methylhexylidene, 3-methylhexylidene, 1-methylhexylidene, 3-ethylpentylidene, 1-ethylpentylidene, 4,4-dimethylpentylidene, 2,4-dimethylpentylidene, 1,2-dimethylpentylidene, 1-propylbutylidene, 2-ethyl-1-methylbutylidene, 1-ethyl-2-methylbutylidene, 1,2,2-trimethylbutylidene, 1,2,3-trimethylbutylidene, 1-pentylethylene, 1-butyl-2-methylethylene, 1-ethyl-2-propylethylene, 1-butyl-1-methylethylene, 1-ethyl-1-propylethylene, 1-butyltrimethylene, 2-butyltrimethylene, 1,3-diethyltrimethylene, 1-methyl-3-propyltrimethylene, 1-propyltetramethylene, 2-propyltetramethylene, 1-ethyl-4-methyltetramethylene, 3-ethyl-1-methyltetramethylene, 1-ethylpentamethylene, 3-ethylpentamethylene, 1,3-dimethylpentamethylene, 1-methylhexamethylene, 3-methylhexamethylene, heptamethylene, octylidene, 6-methylheptylidene, 4-methylheptylidene, 2-methylheptylidene, 1-methylheptylidene, 4-ethylhexylidene, 3-ethylhexylidene, 2-ethylhexylidene, 1-ethylhexylidene, 3,5-dimethylhexylidene, 4,5-dimethylhexylidene, 2,4-dimethylhexylidene, 1,5-dimethylhexylidene, 1,4-dimethylhexylidene, 2-propylpentylidene, 1-propylpentylidene, 2-ethyl-4-methylpentylidene, 3-ethyl-2-methylpentylidene, 3-ethyl-1-methylpentylidene, 1-ethyl-3-methylpentylidene, 3-methyl-1-propylbutylidene, 2-methyl-1-propyl-butylidene, 1-ethyl-2,3-dimethylbutylidene, 1,2-diethylbutylidene, 1-hexylethylene, 1-methyl-2-pentylethylene, 1-butyl-2-ethylethylene, 1,2-dipropylethylene, 1-pentyltrimethylene, 2-pentyltrimethylene, 1-butyl-3-methyltrimethylene, 1-butyl-2-methyltrimethylene, 1-ethyl-3-propyl-trimethylene, 1,2-dimethyl-3-propyltrimethylene, 1-butyltetramethylene, 1-methyl-4-propyltetramethylene, 1-propylpentamethylene, 3-propylpentamethylene, 2-ethyl-4-methylpentamethylene, 1-ethylhexamethylene, 3-ethylhexamethylene, 1,3-dimethylhexamethylene, 1-methylheptamethylene, 4-methylheptamethylene and octamethylene groups.

The alkylene group represented by X, including those alkylene groups exemplified above, may be unsubstituted or may have at least 1, preferably from 1 to 4 and more preferably 1 or 2, substituents selected from the following groups:

hydroxy groups;

C_1-C_4 alkoxy groups, for example the methoxy or ethoxy groups;

aryloxy groups in which the aryl ring has from 6 to 14, more preferably from 6 to 10, ring carbon atoms and which is unsubstituted or has from 1 to 5, more preferably from 1 to 3, substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups, for example the phenoxy, p-tolyloxy, 4-hydroxyphenoxy, 4-aminophenoxy and 4-methoxyphenoxy groups;

C_7-C_9 aralkyloxy groups in which the aryl ring is unsubstituted or has from 1 to 5, more preferably from 1 to 3, substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups, for example the benzyloxy, 4-methylbenzyloxy, 4-hydroxybenzyloxy, 4-aminobenzyloxy and 4-methoxybenzyloxy groups;

mercapto groups;

C_1-C_4 alkylthio groups, for example the methylthio or ethylthio groups;

arylthio groups in which the aryl ring has from 6 to 14, more preferably from 6 to 10, ring carbon atoms and which is unsubstituted or has from 1 to 5, more preferably from 1 to 3, substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups, for example the phenylthio, p-tolylthio, 4-hydroxyphenylthio, 4-aminophenylthio and 4-methoxyphenylthio groups;

C_7-C_9 aralkylthio groups in which the aryl ring is unsubstituted or has from 1 to 5, more preferably from 1 to 3, substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups, for example the benzylthio, 4-methylbenzylthio, 4-hydroxybenzylthio, 4-aminobenzylthio and 4-methoxybenzylthio groups;

carboxyalkylthio groups having from 1 to 4 carbon atoms in the alkyl moiety, for example the carboxymethylthio and carboxyethylthio groups;

amino groups;

amino groups having one or two C_1-C_4 alkyl substituents, for example the methylamino, ethylamino and dimethylamino groups;

amino groups having one or two aryl substituents, wherein the aryl ring has from 6 to 14 ring carbon atoms and is unsubstituted or has from 1 to 5, preferably from 1 to 3, substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups, and C_1-C_4 alkoxy groups, such as the phenylamino, p-tolylamino, 4-hydroxyphenylamino, 4-aminophenylamino and 4-methoxyphenylamino groups;

amino groups having one or two C_7-C_9 aralkyl substituents wherein the aryl moiety is unsubstituted or has from 1 to 5, preferably from 1 to 3, substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkyl groups, such as the benzylamino, 4-methylbenzylamino, 4-hydroxybenzylamino, 4-aminobenzylamino and 4-methoxybenzylamino groups;

amino groups substituted by one or two carboxylic acyl groups as defined in relation to R^2;

aryl groups having from 6 to 14 ring carbon atoms, and being unsubstituted or having from 1 to 5, preferably from 1 to 3, substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups;
carboxy groups;
amidino groups;
sulpho groups;
C_1-C_4 alkylsulphinyl groups, such as the methanesulphinyl or ethanesulphinyl groups;
C_1-C_4 alkylsulphonyl groups, such as the methanesulphonyl or ethanesulphonyl groups; and
heterocyclic groups, such as the pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolazinyl, indolyl and indazolyl groups.

Preferred groups which may be represented by X include C_1-C_5 alkylene groups which are unsubstituted or have one or two substituents selected from: hydroxy groups; C_1-C_4 alkoxy groups; aryloxy groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; C_7-C_9 aralkyloxy groups, wherein the aryl moiety is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; mercapto groups; C_1-C_4 alkylthio groups; arylthio groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; C_7-C_9 aralkylthio groups wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups;
carboxyalkylthio groups in which the alkyl part has from 1 to 4 carbon atoms; amino groups; amino groups having one or two C_1-C_4 alkyl substituents; amino groups having one or two aryl substituents in which the aryl ring has from 6 to 14 ring carbon atoms and is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; amino groups having one or two C_7-C_9 aralkyl substituents in which the aryl part is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; amino groups having one or two carboxylic acyl substituents as defined in relation to R^2; aryl groups having from 6 to 14 ring carbon atoms and being unsubstituted or having from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms.

More preferred groups which may be represented by X are C_1-C_5 alkylene groups which are unsubstituted or have 1 or 2 substituents selected from: hydroxy groups; C_1-C_4 alkoxy groups; mercapto groups; C_1-C_4 alkylthio groups; amino groups; amino groups having one or two C_1-C_4 alkyl substituents; amino groups having one or two carboxylic acyl substituents as defined for R^2; aryl groups having from 6 to 14 carbon atoms wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen hetero-atoms.

Preferred amino acids which may be represented by formula (II) include glycine, β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, 8-aminooctanoic acid, alanine, 2-aminobutyric acid, norvaline, valine, leucine, isoleucine, norleucine, tyrosine, O-methyltyrosine, aspartic acid, glutamic acid, 4-carboxyglutamic acid, 3-methylaspartic acid, 2-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid, 3-hydroxyaspartic acid, 3-hydroxyglutamic acid, 2,3-diaminopropionic acid, 2,4-diaminobutyric acid, 5-hydroxylysine, arginine, N^{δ},N^{δ}-dimethylornithine, N^{ϵ}-methyllysine, cysteine, methionine, ethionine, S-carboxymethylcysteine, S-benzylcysteine, methionine S-oxide, ethionine S-oxide, methionine S,S-dioxide, cysteic acid, serine, O-methylserine, threonine, O-methylthreonine, homothreonine, ethoxinine (= 2-amino-4-ethoxybutyric acid), 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, tryptophan, 2-methylalanine, 2-methylserine, 2-hydroxyisoleucine, 2-methylmethionine, 2-ethyl-2-phenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid, 3-amino-3-phenylpropionic acid, 3-amino-2-hydroxypropionic acid and 4-amino-3-hydroxybutyric acid.

More preferred amino acids are glycine, β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, 8-aminooctanoic acid, alanine, norvaline, valine, leucine, isoleucine, norleucine, N^{δ},N^{δ}-dimethylornithine, methionine, ethionine, O-methylserine, O-methylthreonine, ethoxinine, 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, 2-methylalanine, 2-methylserine, 2-hydroxyisoleucine, 2-ethylphenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid and 3-amino-3-phenylpropionic acid.

The most preferred amino acids are β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, alanine, valine, leucine, norleucine, methionine, histidine and glycine.

When the amino acid derivative is an oligopeptide compound, such as a dipeptide or tripeptide, this type of compound is preferably formed by suitable combination of such amino acids as glycine, β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, alanine, valine, leucine, norleucine, phenylglycine, phenylalanine, methionine and histidine. Examples include leucylglycine, glycyl-β-alanine, glycylalanine, valylalanine, leucylalanine, glycylvaline, alanylvaline, leucylvaline, valylleucine, phenylalanylleucine, histidylleucine, glycylphenylalanine, alanylphenylalanine, leucylphenylalanine, glycylmethionine, valylmethionine, glycylhistidine, alanylvalylglycine, glycylalanylvaline, glycylphenylalanylleucine and glycylglycylhistidine.

Specific examples of the amino acid compounds which may be employed in the present invention are given in the following list. It should, of course, be appreciated that these compounds can exist in the D-, L- and DL-forms and any of these forms can be employed. The compounds are hereinafter referred to by the numbers appended to them in this list. In the case of the amino acids having 2 or more amino grups (e.g. 2,3-diaminopropionic acid, 2,4-diaminobutyric acid and arginine), mono-acylated derivatives (in which the acyl group can be on any amino group) and polyacylated derivatives are possible.

1. Glycine derivatives.

1-1. N-hexanoylglycine
1-2. N-heptanoylglycine
1-3. N-octanoylglycine
1-4. N-nonanoylglycine
1-5. N-decanoylglycine
1-6. N-(o-toluoyl)glycine
1-7. N-(4-methoxybenzoyl)glycine
1-8. N-(1-naphthoyl)glycine
1-9. N-(1-phenyl-1-cyclohexanecarbonyl)glycine
1-10. N-(α,α-diphenylacetyl)glycine
1-11. N-(α-phenyl-α-cyclopentylacetyl)glycine
1-12. N-butoxycarbonylglycine
1-13. N-octanoylleucylglycine
1-14. N-benzoylleucylglycine
1-15. N-butoxycarbonylleucylglycine
1-16. N-octanoylalanylvalylglycine
1-17. N-benzoylalanylvalylglycine
1-18. N-cyclohexanecarbonylalanylvalylglycine
1-19. N-butoxycarbonylalanylvalylglycine

3. β-Alanine derivatives.

2-1. N-hexanoyl-β-alanine
2-2. N-heptanoyl-β-alanine
2-3. N-octanoyl-β-alanine
2-4. N-nonanoyl-β-alanine
2-5. N-(o-toluoyl)-β-alanine
2-6. N-(4-methoxybenzoyl)-β-alanine
2-7. N-(3-hydroxy-2-naphthoyl)-β-alanine
2-8. N-(1-phenyl-1-cyclopentanecarbonyl)-β-alanine
2-9. N -(α-α-diphenylacetyl)-β-alanine
2-10. N(3-phenylpropionyl)-β-alanine
2.11. N-(4-phenylbutyryl)-β-alanine
2.12. N-(4-methoxyphenylacetyl)-β-alanine
2-13. N-t-butoxycarbonyl-β-alanine
2-14. N-benzyloxycarbonyl-β-alanine
2-15. N-(4-methoxybenzyloxycarbonyl)-β-alanine
2-16. N-(4-methylbenzyloxycarbonyl)-β-alanine
2-17. N-(α-methylbenzyloxycarbonyl)-β-alanine

2-18. N -benzoylglycyl-β-alanine
2-19. N-(1-naphthoyl)glycyl-β-alanine
2-20. N-cyclohexanecarbonylglycyl-β-alanine
2-21. N-benzyloxycarbonylglycyl-β-alanine
2-22. N-benzoyl-β-alanine

4-Aminobutyric acid derivatives.

3-1. N-hexanoyl-4-aminobutyric acid
3-2. N-heptanoyl-4-aminobutyric acid
3-3. N-benzoyl-4-aminobutyric acid
3-4. N-(p -toluoyl)-4-aminobutyric acid
3-5. N-(3-methoxybenzoyl)-4-aminobutyric acid
3-6. N-cyclopentanecarbonyl-4-aminobutyric acid
3-7. N-cyclohexanecarbonyl-4-aminobutyric acid
3-8. N-(1-phenyl-1-cyclopropanecarbonyl)-4-aminobutyric acid
3-9. N-(1-phenyl-1-cyclopentanecarbonyl)-4-aminobutyric acid
3-10. N-phenylacetyl-4-aminobutyric acid
3-11. N-(3-phenylpropionyl)-4-aminobutyric acid
3-12. N-(p-tolylacetyl)-4-aminobutyric acid
3-13. N-nicotinoyl-4-aminobutyric acid
3-14. N-butoxycarbonyl-4-aminobutyric acid
3-15. N-benzyloxycarbonyl-4-aminobutyric acid
3-16. N-(3-phenylpropoxycarbonyl)-4-aminobutyric acid
3-17. N-(α-methylbenzyloxycarbonyl-4-aminobutyric acid
3-18. N-(1-naphthoyl)-4-aminobutyric acid

4. 5-Aminovaleric acid derivatives

4-1. Nbutyryl-5-aminovaleric acid
4-2. N-isobutyryl-5-aminovaleric acid
4-3. Nvaleryl-5-aminovaleric acid
4-4. N-isovaleryl-5-aminovaleric acid
4-5. N -hexanoyl-5-aminovaleric acid
4-6. N-benzoyl-5-aminovaleric acid
4-7. N-(m -toluoyl)-5-aminovaleric acid
4-8. N-(2-methoxybenzoyl)-5-aminovaleric acid
4-9. N-cyclopentanecarbonyl-5-aminovaleric acid
4-10. N-cyclohexanecarbonyl-5-aminovaleric acid
4-11. N-(1-phenyl-1-cyclopropanecarbonyl)-5-aminovaleric acid
4-12. N-(1-phenyl-1-cyclohexanecarbonyl)-5-aminovaleric acid.
4-13. N-phenylacetyl-5-aminovaleric acid
4-14. N-(α-phenyl-α-methylacetyl)-5-aminovaleric acid
4-15. N-nicotinoyl-5-aminovaleric acid
4-16. N-(2-thiophenecarbonyl)-5-aminovaleric acid
4-17. N-(2-furoyl)-5-aminovaleric acid
4-18. N-isopropoxycarbonyl-5-aminovaleric acid
4-19. N-pentyloxycarbonyl-5-aminovaleric acid
4-20. N-benzyloxycarbonyl-5-aminovaleric acid
4-21. N-(4-methoxybenzyloxycarbonyl)-5-aminovaleric acid
4-22. N-4-methylbenzyloxycarbonyl)-5-aminovaleric acid
4-23. N-4-hydroxyphenylacetyl)-5-aminovaleric acid
4-24.N(N-methylnicotinoyl)-5-aminovaleric acid

5. 6-Aminohexanoic acid derivatives.

5-1. N -acetyl-6-aminohexanoic acid
5-2. N-propionyl-6-aminohexanoic acid
5-3. N-butyryl-6-aminohexanoic acid
5-4. N-isobutyryl-6-aminohexanoic acid
5-5. N-isovaleryl-6-aminohexanoic acid
5-6. N-hexanoyl-6-aminohexanoic acid
5-7. N-acryloyl-6-aminohexanoic acid
5-8. N-methacryloyl-6-aminohexanoic acid
5-9. N-crotonoyl-6-aminohexanoic acid
5-10. N-propioloyl-6-aminohexanoic acid
5-11. N-benzoyl-6-aminohexanoic acid
5-12. N-(o -toluoyl)-6-aminohexanoic acid
5-13. N-(4-methoxybenzoyl)-6-aminohexanoic acid
5-14. N-(4-aminobenzoyl)-6-aminohexanoic acid
5-15. N-(1-naphthoyl)-6-aminohexanoic acid
5-16. N-cyclobutanecarbonyl-6-aminohexanoic acid
5-17. N-cyclopentanecarbonyl-6-aminohexanoic acid
5-18. N-cyclohexanecarbonyl-6-aminohexanoic acid
5-19. N-phenylacetyl-6-aminohexanoic acid
5-20. N-(3-phenylpropionyl)-6-aminohexanoic acid
5-21. N-nicotinoyl-6-aminohexanoic acid
5-22. N-(2-thiophenecarbonyl)-6-aminohexanoic acid
5-23. N-methoxycarbonyl-6-aminohexanoic acid
5-24. N-ethoxycarbonyl-6-aminohexanoic acid
5-25. N -butoxycarbonyl-6-aminohexanoic acid
5-26. N -pentyloxycarbonyl-6-aminohexanoic acid
5-27. N -benzyloxycarbonyl-6-aminohexanoic acid
5-28. N -phenethyloxycarbonyl-6-aminohexanoic acid
5-29. N-(3-phenylpropoxycarbonyl)-6-aminohexanoic acid
5-30. N-(4-methoxybenzyloxycarbonyl)-6-aminohexanoic acid
5-31. N-(4-methylbenzyloxycarbonyl)-6-aminohexanoic acid
5-32. N-(α-methylbenzyloxycarbonyl)-6-aminohexanoic acid
5-33. N-(N-methylnicotinoyl)-6-aminohexanoic acid
5-34. N-(4-chlorophenylacetyl)-6-aminohexanoic acid

6. 8-Aminooctanoic acid derivatives.

6-1. N-acetyl-8-aminooctanoic acid
6-2. N-valeryl-8-aminooctanoic acid
6-3. N-benzoyl-8-aminooctanoic acid
6-4. N -(3-hydroxybenzoyl)-8-aminooctanoic acid
6-5. N -(3-sulphobenzoyl)-8-aminooctanoic acid
6-6. N -cyclopropanecarbonyl-8-aminooctanoic acid
6-7. N -(4-aminophenylacetyl)-8-aminooctanoic acid
6-8. N-methoxycarbonyl-8-aminooctanoic acid
6-9. N -propoxycarbonyl-8-aminooctanoic acid
6-10. N -isopropoxycarbonyl-8-aminooctanoic acid
6-11. N -benzyloxycarbonyl-8-aminooctanoic acid
6-12. N -(4-hydroxybenzyloxycarbonyl)-8-aminooctanoic acid
6-13. N-(N-methylnicotinoyl)-8-aminooctanoic acid
6-14. N-(6-hydroxynicotinoyl)-8-aminooctanoic acid

7. Alanine derivatives.

7-1. N-valerylalanine
7-2. N-hexanoylalanine
7-3. N-benzoylalanine
7-4. N-(4-methoxybenzoyl)alanine
7-5. N-(1-naphthoyl)alanine
7-6. N-(1-phenyl-1-cyclopropanecarbonyl)alanine
7-7. N-phenylacetylalanine
7-8. N-butoxycarbonylalanine
7-9. N-benzyloxycarbonylalanine
7-10. N-(α-methylbenzyloxycarbonyl)alanine
7-11. N-octanoylglycylalanine
7-12. N -benzoylglycylalanine
7-13. N-butoxycarbonylglycylalanine
7-14. N-benzoylvalylalanine
7-15. N-(p-toluoyl)valylalanine
7-16. N-cyclopentanecarbonylvalylalanine
7-17. N-cyclohexanecarbonylvalylalanine
7-18. N-benzyloxycarbonylvalylalanine
7-19. N-benzoylleucylalanine
7-20. N-(4-methoxybenzoyl)leucylalanine
7-21. N-butoxycarbonylleucylalanine
7-22. N-benzyloxycarbonylleucylalanine
7-23. N-(2-bromobenzoyl)alanine

8. 2-Aminobutyric acid derivatives.

8-1. N-pivaloyl-2-aminobutyric acid
8-2. N-hexanoyl-2-aminobutyric acid
8-3. N-heptanoyl-2-aminobutyric acid
8-4. N-benzoyl-2-aminobutyric acid
8-5. N-(p -toluoyl)-2-aminobutyric acid
8-6. N-(1-phenyl-1-cyclopentanecarbonyl)-2-aminobutyric acid
8-7. N-(α,α-diphenylacetyl)-2-aminobutyric acid
8-8. N-ethoxycarbonyl-2-aminobutyric acid
8-9. N-benzyloxycarbonyl-2-aminobutyric acid
8-10. N-(4-methoxybenzyloxycarbonyl-2-aminobutyric acid

9. Norvaline derivatives.

9-1. N-valerylnorvaline
9-2. N-decanoylnorvaline
9-3. N-benzoylnorvaline
9-4. N-(m-toluoyl)norvaline
9-5. N-(3-sulphobenzoyl)norvaline
9-6. N -cyclohexanecarbonylnorvaline
9-7. N-(1-phenyl-1-cyclohexanecarbonyl)norvaline
9-8. N-(α-phenyl-α-ethylacetyl)norvaline
9-9. N-(4-methoxyphenylacetyl)norvaline
9-10. N -(2-pyrazinecarbonyl)norvaline
9-11. N-benzyloxycarbonylnorvaline
9-12. N-(4-methylbenzyloxycarbonyl)norvaline

Valine derivatives.

10-1. N-propionylvaline
10-2. N-butyrylvaline
10-3. N-isobutyrylvaline
10-4. N -valerylvaline
10-5. N-acryloylvaline
10-6. N-methacryloylvaline
10-7. N-crotonoylvaline
10-8. N-propioloylvaline
10-9. N-(2-methoxybenzoyl)valine
10-10. N-(4-butoxybenzoyl)valine
10-11. N-cyclopentanecarbonylvaline
10-12. N-cyclohexanecarbonylvaline
10-13. N-(1-phenyl-1-cyclopentanecarbonyl)valine
10-14. N-phenylacetylvaline
10-15. N-nicotinoylvaline
10-16. N-(2-piperidinecarbonyl)valine
10-17. N-ethoxycarbonylvaline
10-18. N-isopropoxycarbonylvaline
10-19. N-t-butoxycarbonylvaline
10-20. N-pentyloxycarbonylvaline
10-21. N-benzyloxycarbonylvaline
10-22. N-(p-p-tolylacetyl)valine
10-23. N-benzoylglycylvaline
10-24. N-(p-toluoyl)glycylvaline
10-25. N-(1-naphthoyl)glycylvaline
10-26. N-cyclopentanecarbonylglycylvaline
10-27. N-butoxycarbonylglycylvaline
10-28. N-octanoylalanylvaline
10-29. N-benzoylalanylvaline
10-30. N-(p-toluoyl)alanylvaline
10-31. N-(4-aminobenzoyl)alanylvaline
10-32. N-(1-naphthoyl)alanylvaline
10-33. N-cyclohexanecarbonylalanylvaline
10-34. N-phenylacetylalanylvaline
10-35. N-benzyloxycarbonylalanylvaline
10-36. N-benzoylleucylvaline
10-37. N-benzoylglycylalanylvaline
10-38. N-(p -toluoyl)glycylalanylvaline
10-39. N-(1-naphthoyl)glycylalanylvaline
10-40. N-cyclopentanecarbonylglycylalanylvaline
10-41. N-butoxycarbonylglycylalanylvaline
10-42. N-benzyloxycarbonylglycylalanylvaline
10-43. N-(N-methylnicotinoyl)valine
10-44. N-(3-fluorobenzoyl)valine
10-45. N-benzoylvaline

11. Leucine derivatives.

11-1. N-butyrylleucine
11-2. N-isovalerylleucine
11-3. N-benzoylleucine
11-4. N-(4-butylbenzoyl)leucine
11-5. N-(2-hydroxybenzoyl)leucine
11-6. N-(3-sulphobenzoyl)leucine
11-7. N -cyclopentanecarbonylleucine

11-8. N-cyclohexanecarbonylleucine
11-9. N-(1-phenyl-1-cyclopropanecarbonyl)leucine
11-10. N-phenylacetylleucine
11-11. N-nicotinoylleucine
11-12. N-ethoxycarbonylleucine
11-13. N-benzyloxycarbonylleucine
11-14. N -(4-hydroxyphenylacetyl)leucine
11-15. N-benzoylvalylleucine
11-16. N-ethoxycarbonylvalylleucine
11-17. N-benzoylphenylalanylleucine
11-18. N-phenylacetylphenylalanylleucine
11-19. N-benzyloxycarbonylphenylalanylleucine
11-20. N-benzoylhistidylleucine
11-21. N-(p-toluoyl)histidylleucine
11-22. N-(4-hydroxybenzoyl)histidylleucine
11-23. N-(1-naphthoyl)histidylleucine
11-24. N-benzoylglycylphenylalanylleucine
11-25. N-(4-methoxybenzoyl)glycylphenylalanylleucine
11-26. N-phenylacetylglycylphenylalanylleucine
11-27. N-t-butoxycarbonylleucine

12. Isoleucine derivatives.

12-1. N-valerylisoleucine
12-2. N-pivaloylisoleucine
12-3. N-octanoylisoleucine
12-4. N-benzoylisoleucine
12-5. N-(3-hydroxybenzoyl)isoleucine
12-6. N-cyclopentanecarbonylisoleucine
12-7. N-cyclohexanecarbonylisoleucine
12-8. N-(1-phenyl-1-cyclopentanecarbonyl)isoleucine
12-9. N -phenylacetylisoleucine
12-10. N-methoxycarbonylisoleucine
12-11. N-propoxycarbonylisoleucine
12-12. N-isopropoxycarbonylisoleucine
12-13. N-benzyloxycarbonylisoleucine

13. Norleucine derivatives.

13-1. N-propionylnorleucine
13-2. N-valerylnorleucine
13-3. N-pivaloylnorleucine
13-4. N-nonanoylnorleucine
13-5. N-benzoylnorleucine
13-6. N-(4-hydroxybenzyl)norleucine
13-7. N-cyclohexanecarbonylnorleucine
13-8. N-(1-phenyl-1-cyclopropanecarbonyl)norleucine
13-9. N -(α-phenyl-α-ethylacetyl)norleucine
13-10. N-ethoxycarbonylnorleucine
13-11. N-propoxycarbonylnorleucine
13-12. N-butoxycarbonylnorleucine
13-13. N-benzyloxycarbonylnorleucine

14. Oligopeptide derivatives

14-1. N-benzoylglycylphenylalanine
14-2. N-(4-hydroxybenzoyl)glycylphenylalanine
14-3. N-(1-naphthoyl)glycylphenylalanine
14-4. N-ethoxycarbonylglycylphenylalanine
14-5. N-benzyloxycarbonylglycylphenylalanine
14-6. N-benzoylalanylphenylalanine
14-7. N-(p -toluoyl)alanylphenylalanine
14-8. N-(4-hydroxybenzoyl)alanylphenylalanine
14-9. N-(4-aminobenzoyl)alanylphenylalanine
14-10. N-(1-naphthoyl)alanylphenylalanine
14-11. N-benzyloxycarbonylalanylphenylalanine
14-12. N-benzoylleucylphenylaline
14-13. N-(4-hydroxybenzoyl)leucyphenylalanine
14-14. N-cyclohexanecarbonylleucylphenylalanine
14-15. N-benzyloxycarbonylleucyphenylalanine

15. Tyrosine derivatives.

15-1. N-benzoyltyrosine
15-2. N-(3-methoxybenzoyl)tyrosine
15-3. N-cyclohexanecarbonyltyrosine
15-4. N-benzyloxycarbonyltyrosine
15-5. N-phenethyloxycarbonyltyrosine

16. O-Methyltyrosine derivatives.

16-1. N-acetyl-O-methyltyrosine
16-2. N-propioloyl-O-methyltyrosine
16-3. N-benzoyl-O -methyltyrosine
16-4. N-(4-aminobenzoyl)-O-methyltyrosine
16-5. N-(1-phenyl-1-cyclopentanecarbonyl)-O-methyltyrosine
16-6. N-(1-phenyl-1-cyclohexanecarbonyl)-O-methyltyrosine
16-7. N-methoxycarbonyl-O -methyltyrosine
16-8. N-benzyloxycarbonyl-O-methyltyrosine
16-9. N-phenylethyloxycarbonyl-O-methyltyrosine

17. Aspartic acid derivatives.

17-1. N-heptanoylaspartic acid
17-2. N-decanoylaspartic acid
17-3. N-(4-hydroxybenzoyl)aspartic acid
17-4. N -(3-hydroxy-2-naphthoyl)aspartic acid
17-5. N -(1-phenyl-1-cyclopentanecarbonyl)aspartic acid
17-6. N-(1-phenyl-1-cyclohexanecarbonyl)aspartic acid
17-7. N-benzyloxycarbonylaspartic acid
17-8. N-(4-methoxybenzyloxycarbonyl)aspartic acid

18. Glutamic acid derivatives.

18-1. N-nonanoylglutamic acid
18-2. N-(4-methoxybenzoyl)glutamic acid
18-3. N-(1-naphthoyl)glutamic acid

18-4. N-(1-phenyl-1-cyclopentanecarbonyl)glutamic acid
18-5. N -benzyloxycarbonylglutamic acid
18-6. N-benzoylglutamic acid

19. 4-Carboxyglutamic acid derivatives.

19-1. N-heptanoyl-4-carboxyglutamic acid
19-2. N-(4-methoxybenzoyl)-4-carboxyglutamic acid
19-3. N-(1-naphthoyl)-4-carboxyglutamic acid
19-4. N-(1-hydroxy-2-naphthoyl)-4-carboxyglutamic acid
19-5. N -phenylacetyl-4-carboxyglutamic acid

20. 3-Methylaspartic acid derivatives.

20-1. N -octanoyl-3-methylaspartic acid
20-2. N-(4-methoxybenzoyl)-3-methylaspartic acid
20-3. N-(α-phenyl-α-cyclopentylacetyl)-3-methylaspartic acid

21. 2-Aminoadipic acid derivatives.

21-1. N-hexanoyl-2-aminoadipic acid
21-2. N-benzoyl-2-aminoadipic acid
21-3. N-(p-toluoyl)-2-aminoadipic acid
21-4. N-(1-naphthoyl)-2-aminoadipic acid
21-5. N-(4-phenylbutyryl)-2-aminoadipic acid
21-6. N-phenylacetyl-2-aminoadipic acid
21-7. N -ethoxycarbonyl-2-aminoadipic acid

22. 2-Aminopimelic acid derivatives.

22-1. N -valeryl-2-aminopimelic acid
22-2. N-benzoyl-2-aminopimelic acid
22-3. N-(3-phenylproplonyl)-2-aminopimelic acid
22-4. N-methoxycarbonyl-2-aminopimelic acid
22-5. N-ethoxycarbonyl-2-aminopimelic acid
22-6. N-benzyloxycarbonyl-2-aminopimelic acid

23. 2-Aminosuberic acid derivatives.

23-1. N -butyryl-2-aminosuberic acid
23-2. N-benzoyl-2-aminosuberic acid
23-2. N-(1-naphthoyl)-2-aminosuberic acid
23-4. N -(α-phenyl-α-cyclopentylacetyl)-2-aminosuberic acid
23-5. N-methoxycarbonyl-2-aminosuberic acid
23-6. N-propoxycarbonyl-2-aminosuberic acid

24. 3-Hydroxyaspartic acid derivatives.

24-1. N-(1-naphthoyl)-3-hydroxyaspartic acid
24-2. N-(1-phenyl-1-cyclohexanecarbonyl)-3-hydroxyaspartic acid

24-3. N-(α-phenyl-α-ethylacetyl)-3-hydroxyaspartic acid

25. 3-Hydroxyglutamic acid derivatives.

25-1. N-(1-naphthoyl)-3-hydroxyglutamic acid
25-2. N-(1-phenyl-1-cyclohexanecarbonyl)-3-hydroxyglutamic acid
25-3. N-(α,α-diphenylacetyl)-3-hydroxyglutamic acid

26. 2,3-Diaminopropionic acid derivatives.

26-1. N^{α}-hexanoyl-2,3-diaminopropionic acid
26-2. N^{α}-(4-butylbenzoyl)-2,3-diaminopropionic acid
26-3. N^{α},N^{β}-dibenzoyl-2,3-diaminopropionic acid
26-4. N^{α}-(1-phenyl-1-cyclopentanecarbonyl)-2,3-diaminopropionic acid
26-5. N^{α}-(α-phenyl-α-ethylacetyl)-2,3-diaminopropionic acid

27. 2,4-Diaminobutyric acid derivatives.

27-1. N^{α}-(1-naphthoyl)-2,4-diaminobutyric acid
27-2. N^{α},N^{γ}-dibenzoyl-2,4-diaminobutyric acid
27-3. N^{α}-(1-phenyl-1-cyclopentanecarbonyl)-2,4-diaminobutyric acid
27-4. N^{α}-(α-phenyl-α-ethylacetyl)-2,4-diaminobutyric acid

28. 5-Hydroxylysine derivatives.

28-1. N^{α}-(p-toluoyl)-5-hydroxylysine
28-2. N^{α},N^{δ}-dibenzoyl-5-hydroxylysine
28-3. N^{α}-(1-phenyl-1-cyclopentanecarbonyl)-5-hydroxylysine
28-4. N^{α}-(α-phenyl-α-cyclopentylacetyl)-5-hydroxylysine
28-5. N^{α}-(1-phenyl-1-cyclopentanecarbonyl)-5-hydroxylysine

29. Arginine derivatives.

29-1. N^{α}-heptanoylarginine
29-2. N^{α}-(2-methoxybenzoyl)arginine

30. N^{δ},N^{δ}-Dimethylornithine derivatives.

30-1. N^{α}-pivaloyl-N^{δ},N^{δ}-dimethylornithine
30-2. N^{α}-octanoyl-N^{δ},N^{δ}-dimethylornithine
30-3. N^{α}-acryloyl-N^{δ},N^{δ}-dimethylornithine
30-4. N^{α}-benzoyl-N^{δ}, N^{δ}-dimethylornithine
30-5. N^{α}-(4-hydroxybenzoyl)-N^{δ},N^{δ}-dimethylornithine
30-6. N^{α}-cyclohexanecarbonyl-N^{δ},N^{δ}-dimethylornithine
30-7. N^{α}-(α-phenyl-α-methylacetyl)-N^{δ},N^{δ}-dimethylornithine
30-8. N^{α}-ethoxycarbonyl-N^{α},N^{α}-dimethylornithine
30-9. N^{α}-butoxycarbonyl-N^{δ},N^{δ}-dimethylornithine
30-10. N^{α}-benzyloxycarbonyl-N^{δ},N^{δ}-dimethylornithine

31. N^{ϵ}-Methyllysine derivatives.

31-1. N^{α}-hexanoyl-N^{ϵ}-methyllysine
31-2. N^{α}-nonanoyl-N^{ϵ}-methyllysine
31-3. N^{α}-acryloyl-N^{ϵ}-methyllysine
31-4. N^{α}-benzoyl-N^{ϵ}-methyllysine
31-5. N^{α}-(4-butoxybenzoyl)-N^{ϵ}-methyllysine
31-6. N^{α}-(3-sulphobenzoyl)-N^{ϵ}-methyllysine
31-7. N^{α}-cyclobutanecarbonyl-N^{ϵ}-methyllysine
31-8. N^{α}-cyclohexanecarbonyl-N^{ϵ}-methyllysine
31-9. N^{α}-phenylacetyl-N^{ϵ}-methyllysine
31-10. N^{α}-propoxycarbonyl-N^{ϵ}-methyllysine
31-11. N^{α}-isopropoxycarbonyl-N^{ϵ}-methyllysine
31-12. N^{α}-benzyloxycarbonyl-N^{ϵ}-methyllysine

32. Cysteine derivatives.

32-1. N-phenylacetylcysteine

33. Methionine derivatives.

33-1. N-valerylmethionine
33-2. N-acryloylmethionine
33-3. N-methacryloylmethionine
33-4. N-benzoylmethionine
33-5. N-(p-toluoyl)methionine
33-6. N-(4-methoxybenzoyl)methionine
33-7. N-(4-aminobenzoyl)methionine
33-8. N-cyclopentanecarbonylmethionine
33-9. N -cyclohexanecarbonylmethionine
33-10. N-(1-phenyl-1-cyclohexanecarbonyl)methionine
33-11. N -phenylacetylmethionine
33-12. N-(α-phenyl-α-methylacetyl)methionine
33-13. N -methoxycarbonylmethionine
33-14. N-ethoxycarbonylmethionine
33-15. N-butoxycarbonylmethionine
33-16. N-benzyloxycarbonylmethionine
33-17. N-(4-methylbenzyloxycarbonyl)methionine
33-18. N-benzoylglycylmethionine
33-19. N-(4-methoxybenzoyl)glycylmethionine
33-20. N-benzyloxycarbonylglycylmethionine
33-21. N-benzoylvalylmethionine
33-22. N-cyclopentanecarbonylvalylmethionine
33-23. N-ethoxycarbonylvalylmethionine

34. Ethionine derivatives.

34-1. N-butyrylethionine
34-2. N-benzoylethionine
34-3. N-(p-toluoyl)ethionine
34-4. N-(m-toluoyl)ethionine
34-5. N -(4-butylbenzoyl)ethionine
34-6. N-(4-hydroxybenzoyl)ethionine
34-7. N-(4-aminobenzoyl)ethionine
34-8. N-(3-sulphobenzoyl)ethionine

34-9. N-(1-phenyl-1-cyclopropanecarbonyl)ethionine
34-10. N -phenylacetylethionine
34-11. N-methoxycarbonylethionine
34-12. N-ethoxycarbonylethionine
34-13. N-benzyloxycarbonylethionine
34-14. N-(4-methoxybenzyloxycarbonyl)ethionine
34-15. N-cyclohexanecarbonylethionine

35. S-Carboxymethylcysteine derivatives.

35-1. N-propionyl-S-carboxymethylcysteine
35-2. N-acryloyl-S-carboxymethylcysteine
35-3. N-benzoyl-S-carboxymethylcysteine
35-4. N-(p-toluoyl)-S-carboxymethylcysteine
35-5. N-(4-methoxybenzoyl)-S-carboxymethylcysteine
35-6. N-(4-butoxybenzoyl)-S-carboxymethylcysteine
35-7. N-cyclohexanecarbonyl-S-carboxymethylcysteine
35-8. N-(1-phenyl-1-cyclopentanecarbonyl)-S-carboxymethylcysteine
35-9. N-(α-methylbenzyloxycarbonyl)-S -carboxymethylcysteine

36. S-Benzylcysteine derivatives.

36-1. N -benzoyl-S-benzylcysteine
36-2. N -(4-hydroxybenzoyl)-S-benzylcysteine
36-3. N-(3-sulphobenzoyl)-S-benzylcysteine
36-4. N-cyclopropanecarbonyl-S-benzylcysteine
36-5. N-methoxycarbonyl-S -benzylcysteine
36-6. N-ethoxycarbonyl-S-benzylcysteine
36-7. N-propoxycarbonyl-S-benzylcysteine
36-8. N -(4-hydroxybenzyloxycarbonyl)-S-benzylcysteine

37. Methionine S-oxide derivatives.

37-1. N-(p-toluoyl)methionine S-oxide
37-2. N-pentyloxycarbonylmethionine S-oxide
37-3. N-benzyloxycarbonylmethionine S-oxide

38. Ethionine S-oxide derivatives.

38-1. N-benzoylethionine S-oxide
38-2. N-benzyloxycarbonylethionine S-oxide

39. Methionine S,S-dioxide derivatives.

39-1. N-(1-napthoyl)methionineS, S-dioxide
39-2. Ncyclohexanecarbonylmethionine S,S-dioxide
39-3. N-pentyloxycarbonylmethionine S, S-dioxide

40. Cysteic acid derivatives.

40-1. N-(p-toluoyl)cysteic acid
40-2. n-(1-napthoyl)cysteic acid

40-3. N-(3-hydroxy-2-napthoyl)cysteic acid
40-4. N-(1-phenyl-1-cyclohexanecarbonyl)cysteic acid

41. Serine derivatives.

41-1. N-octanoylserine
41-2. N-benzoylserine
41-3. N-(m-toluoyl)serine
41-4. N-(4-methoxybenzoyl)serine
41-5. N-(1-napthoyl)serine
41-6. N-(1-phenyl-1-cyclopentanecarbonyl)serine
41-7. N-benzyloxycarbonylserine
41-8. N-(α-methylbenzyloxycarbonyl)serine

42. O-methylserine derivatives.

42-1. N-valeryl-O-methylserine
42-2. N-benzoyl-O-methylserine
42-3. N-cyclohexanecarbonyl-O-methylserine
42-4. N-phenylacetyl-O-methylserine
42-5. N-(α-phenyl-α-methylacetyl)-O-methylserine
42-6. N-(3-phenylpropionyl)-O-methylserine
42-7. N-phenethyloxycarbonyl-O-methylserine

43. Threonine derivatives.

43-1. N-hexanoylthreonine
43-2. N-nonanoylthreonine
43-3. N-benzoylthreonine
43-4. N-(3-hydroxy-2-naphthoyl)threonine
43-5. N-cyclohexanecarbonylthreonine
43-6. N-(α,α-diphenylacetyl)threonine
43-7. N-butoxycarbonylthreonine
43-8. N-benzyloxycarbonylthreonine
43-9. N-(4-methoxybenzyloxycarbonyl)threonine

44. O-Methylthreonine derivatives.

44-1. N -butyryl-O-methylthreonine
44-2. N -(4-methoxybenzyoyl)-O-methylthreonine
44-3. N-(1-naphthoyl)-O-methylthreonine
44-4. N-(1-phenyl-1-cyclopentanecarbonyl)-O-methylthreonine
44-5. N-ethyoxycarbonyl-O -methylthreonine
44-6. N-(3-phenylpropoxycarbonyl)-O-methylthreonine

45. Homoserine derivatives.

45-1. N-heptanoylhomoserine
45-2. N-benzoylhomoserine
45-3. N-(3-methoxybenzoyl)homoserine
45-4. N-(α-phenyl-α-cyclopentylacetyl)homoserine
45-5. N -(4-hydroxybenzyloxycarbonyl)homoserine

45-6. N -(4-methylbenzyloxycarbonyl)homoserine

46. Ethoxinine derivatives.

46-1. N-benzoylethoxinine
46-2. N-(4-butoxybenzoyl)ethoxine
46-3. N-cyclohexanecarbonylethoxinine
46-4. N-methoxycarbonylethoxinine

47. 3-Methoxyvaline derivatives.

47-1. N-isovaleryl-3-methoxyvaline
47-2. N-(p-toluoyl)-3-methoxyvaline
47-3. N-(1-naphthoyl)-3-methoxyvaline
47-4. N-cyclopentanecarbonyl-3-methoxyvaline
47-5. N-cyclohexanecarbonyl-3-methoxyvaline
47-6. N-methoxycarbonyl-3-methoxyvaline
47-7. N-ethoxycarbonyl-3-methoxyvaline

48. 3-Phenylserine derivatives.

48-1. N-propionyl-3-phenylserine
48-2. N-(4-aminobenzoyl)-3-phenylserine
48-3. N-(1-naphthoyl)-3-phenylserine
48-4. N-benzoyl-3-phenylserine
48-5. N-cyclohexanecarbonyl-3-phenylserine
48-6. N-phenylacetyl-3-phenylserine
48-7. N-methoxycarbonyl-3-phenylserine
48-8. N-butoxycarbonyl-3-phenylserine
48-9. N-benzyloxycarbonyl-3-phenylserine
48-10. N-(α-methylbenzyloxycarbonyl)-3-phenylserine

49. 3-Methyl-3-phenylalanine derivatives.

49-1. N-acetyl-3-methyl-3-phenylalanine
49-2. N -hexanoyl-3-methyl-3-phenylalanine
49-3. N-benzoyl-3-methyl-3-phenylalanine
49-4. N -(4-aminobenzoyl)-3-methyl-3-phenylalanine
49-5. N-(3-sulphobenzoyl)-3-methyl-3-phenylalanine
49-6. N-cyclobutanecarbonyl-3-methyl-3-phenylalanine
49-7. N-cyclopentanecarbonyl-3-methyl-3-phenylalanine
49-8. N-phenylacetyl-3-methyl-3-phenylalanine
49-9. N-isopropoxycarbonyl-3-methyl-3-phenylalanine
49-10. N-butoxycarbonyl-3-methyl-3-phenylalanine
49-11. N-(4-aminobenzyloxycarbonyl)-3-methyl-3-phenylalanine

50. Histidine derivatives.

50-1. N -acetylhistidine
50-2. N-hexanoylhistidine
50-3. N-acryloylhistidine
50-4. N-methacryloylhistidine
50-5. N-benzoylhistidine

50-6. N-(p-toluoyl)histidine
50-7. N-(4-methoxybenzoyl)histidine
50-8. N-(4-butoxybenzoyl)histidine
50-9. N-cyclopentanecarbonylhistidine
50-10. N-cyclohexanecarbonylhistidine
50-11. N-(1-phenyl-1-cyclopentanecarbonyl)histidine
50-12. N -phenylacetylhistidine
50-13. N-(α-phenyl-α-cyclopentylacetyl)histidine
50-14. N -(4-methoxybenzyloxycarbonyl)histidine
50-15. N-benzoylglycylhistidine
50-16. N -(4-butylbenzoyl)glycylhistidine
50-17. N-phenylacetylglycylhistidine
50-18. N-ethoxycarbonylglycylhistidine
50-19. N-benzyloxycarbonylglycylhistidine
50-20. N-benzoylglycylglyclhistidine
50-21. N-ethoxycarbonylglycylglycylhistidine
50-22. N-benzyloxycarbonylglycylglycylhistidine
50-23. N-t-butoxycarbonylhistidine

51. Tryptophan derivatives.

51-1. N-(4-hydroxybenzoyl)trytophan
51-2. N-benzyloxycarbonyltrytophan

52. 2-Methylalanine derivatives.

52-1. N-propionyl-2-methylalanine
52-2. N-benzoyl-2-methylalanine
52-3. N-(m-toluoyl)-2-methylalanine
52-4. N-(3-methoxybenzoyl)-2-methylalanine
52-5. N-cyclobutanecarbonyl-2-methylalanine
52-6. N-phenylacetyl-2-methylalanine
52-7. N-phenethyloxycarbonyl-2-methylalanine

53. 2-Methylserine derivatives.

53-1. N-valeryl-2-methylserine
53-2. N-octanoyl-2-methylserine
53-3. N-benzoyl-2-methylserine
53-4. N-(o-toluoyl)-2-methylserine
53-5. N-(4-methoxybenzoyl)-2-methylserine
53-6. N-(1-naphthoyl)-2-methylserine
53-7. N-cyclopentanecarbonyl-2-methylserine
53-8. N-(α,α-diphenylacetyl)-2-methylserine
53-9. N -pentyloxycarbonyl-2-methylserine

54. 2-Hydroxyisoleucine derivatives.

54-1. N -valeryl-2-hydroxyisoleucine
54-2. N-heptanoyl-2-hydroxyisoleucine
54-3. N-benzoyl-2-hydroxyisoleucine
54-4. N-(4-butylbenzoyl)-2-hydroxyisoleucine
54-5. N-(3-hydroxy-2-naphthoyl)-2-hydroxyisoleucine
54-6. N -cyclohexanecarbonyl-2-hydroxyisoleucine

54-7. N -phenylacetyl-2-hydroxyisoleucine

55. 2-Methylmethionine derivatives.

55-1. N -hexanoyl-2-methylmethionine
55-2. N-benzoyl-2-methylmethionine
55-3. N-(4-hydroxybenzoyl)-2-methylmethionine
55-4. N-propoxycarbonyl-2-methylmethionine
55-5. N -isopropoxycarbonyl-2-methylmethionine

56. 2-Ethyl-2-phenylglycine derivatives.

56-1. N-acetyl-2-ethyl-2-phenylglycine
56-2. N-butyryl-2-ethyl-2-phenylglycine
56-3. N-(3-sulphobenzoyl)-2-ethyl-2-phenylglycine
56-4. N-ethoxycarbonyl-2-ethyl-2-phenylglycine
56-5. N-propoxycarbonyl-2-ethyl-2-phenylglycine

57. 3-Aminobutyric acid derivatives.

57-1. N -hexanoyl-3-aminobutyric acid
57-2. N-benzoyl-3-aminobutyric acid
57-3. N-(4-methoxybenzoyl)-3-aminobutyric acid
57-4. N-(3-sulphobenzoyl)-3-aminobutyric acid
57-5. N-(1-naphthoyl)-3-aminobutyric acid
57-6. N-cyclopropanecarbonyl-3-aminobutyric acid
57-7. N-(α,α-diphenylacetyl)-3-aminobutyric acid
57-8. N -(4-phenylbutyl)-3-aminobutyric acid
57-9. N -(α-methylbenzyloxycarbonyl)-3-aminobutyric acid

58. 3-Amino-4-methylvaleric acid derivatives.

58-1. N-valeryl-3-amino-4-methylvaleric acid
58-2. N-isovaleryl-3-amino-4-methylvaleric acid
58-3. N-heptanoyl-3-amino-4-methylvaleric acid
58-4. N-benzoyl-3-amino-4-methylvaleric acid
58-5. N-(m-toluoyl)-3-amino-4-methylvaleric acid
58-6. N-(3-sulphobenzoyl)-3-amino-4-methylvaleric acid
58-7. N-(1-naphthoyl)-3-amino-4-methylvaleric acid
58-8. N-phenylacetyl-3-amino-4-methylvaleric acid
58-9. N-(3-phenylpropionyl)-3-amino-4-methylvaleric acid
58-10. N-butoxycarbonyl-3-amino-4-methylvaleric acid
58-11. N-(4-methylbenzyloxycarbonyl)-3-amino-4-methylvaleric acid

59. 3-Amino-3-phenylpropionic acid derivatives.

59-1. N-butyryl-3-amino-3-phenylpropionic acid
59-2. N-valeryl-3-amino-3-phenylpropionic acid
59-3. N-benzoyl-3-amino-3-phenylpropionic acid
59-4. N-(4-aminobenzoyl)-3-amino-3-phenylpropionic acid
59-5. N-cyclopropanecarbonyl-3-amino-3-phenylpropionic acid
59-6. N-cyclobutanecarbonyl-3-amino-3-phenylpropionic acid
59-7. N-cyclopentanecarbonyl-3-amino-3-phenylpropionic acid

59-8. N-methoxycarbonyl-3-amino-3-phenylpropionic acid
59-9. N-propoxycarbonyl-3-amino-3-phenylpropionic acid
59-10. N -butoxycarbonyl-3-amino-3-phenylpropionic acid
59-11. N-(4-aminobenzyloxycarbonyl)-3-amino-3-phenyl-propionic acid

60. 3-Amino-2-hydroxypropionic acid derivatives.

60-1. N-valeryl-3-amino-2-hydroxypropionic acid
60-2. N-heptanoyl-3-amino-2-hydroxypropionic acid
60-3. N-benzoyl-3-amino-2-hydroxypropionic acid
60-4. N-(3-methoxybenzoyl)-3-amino-2-hydroxypropionic acid
60-5. N-cyclohexanecarbonyl-3-amino-2-hydroxypropionic acid
60-6. N-benzyloxycarbonyl-3-amino-2-hydroxypropionic acid
60-7. N-(3-phenylpropoxycarbonyl)-3-amino-2-hydroxypropionic acid

61. 4-Amino-3-hydroxybutyric acid derivatives

61-1. N-isobutyryl-4-amino-3-hydroxybutyric acid
61-2. N-decanoyl-4-amino-3-hydroxybutyric acid
61-3. N-benzoyl-4-amino-3-hydroxybutyric acid
61-4. N-(o-toluoyl)-4-amino-3-hydroxybutyric acid
61-5. N-(3-aminobenzoyl)-4-amino-3-hydroxybutyric acid
61-6. N -(1-phenyl-1-cyclohexanecarbonyl)-4-amino-3-hydroxybutyric acid
61-7. N-(α-phenyl-α-methylacetyl)-4-amino-3-hydroxybutyric acid
61-8. N-(4-methoxybenzyloxycarbonyl)-4-amino-3-hydroxybutyric acid

Of the amino acid derivatives listed above, the following are particularly preferred: Compounds No. 2-5, 2-6, 2-7, 2-18, 2-22, 4-6, 5-11, 5-18, 5-33, 6-3, 7-3, 7-5, 7-14, 8-4, 9-3, 10-4, 10-29, 10-45, 11-3, 11-24, 13-5, 14-1, 14-6, 14-14, 16-3, 33-4, 33-11, 33-21, 34-2, 34-14, 43-3, 50-5, 50-6, 50-7, 57-3 and 59-1. Of these, Compounds No. 2-22 and 10-45, especially No. 2-22, are most preferred.

The amino acid derivatives employed in the present invention are acids and, as such, are capable of forming salts; any pharmaceutically acceptable salt of these amino acids may be employed. Examples of such salts include: alkali metal salts such as the sodium or potassium salts; alkaline earth metal salts, such as the calcium salt; other metal salts, such as the magnesium, aluminium, iron, zinc, copper, nickel and cobalt salts; the ammonium salt; and salts with amino sugars, such as glucosamine and galactosamine.

The compositions of the invention may be prepared by any suitable method which involves mixing the antibiotic with the amino acid derivative and the invention is not intended to be limited by any particular method of preparation. Since the amino acid derivatives employed in this invention have, in general, very limited solubility in water, it is preferred that they should first be dispersed in water and then converted to a suitable salt by adding an aqueous solution of an appropriate base, for example: a metal compound, such as sodium hydroxide or potassium hydroxide; ammonia; or an amino sugar, such as glucosamine or galactosamine. Sufficient of the base is preferably added to adjust the pH of the mixture to a value within the range from 5.5 to 9, more preferably from 6 to 9.

The penem or carbapenem antibiotic is then added to the resulting solution. The mixed solution thus obtained may be employed as such or it may first be lyophilized to give a powdery mixture, which may be subsequently formulated into an appropriate dosage form suitable for the chosen route of administration, either by the manufacturer or prior to use.

The above mixing and preparation steps may take place at any temperature at which the components are fluid (especially the media) and are not decomposed, e.g. from 0 to 100°C, more conveniently from 0 to 50°C and most conveniently at about ambient temperature.

Although it is convenient to administer the antibiotic and the amino acid derivative simultaneously in a single composition, it is, of course, clear that the two compounds may be administered separately, provided that they are administered sufficiently closely in time to each other that the amino acid derivative has a suitable concentration in the blood for all or most of the time that the antibiotic is present. Normally, it is anticipated that this will be achieved if the two compounds are administered within about one hour of each other, the amino acid preferably being administered before the antibiotic.

The composition of the invention is particularly suitable for use by intravenous administration.

There is no particular restriction on the relative proportions of the amino acid derivative and the penem or carbapenem antibiotic; in general, we have found that weight proportions of amino acid derivative to antibiotic of from 0.1:1 to 4:1 give good results, but equally proportions outside this range may successfully be employed. Approximately equal weights are generally most convenient.

The invention is further illustrated by the following Examples and Activity Tests. In the following, the penem or carbapenem antibiotics are referred to by the numbers appended to them in the foregoing list and are identified as "(Carba)-Penem Cpd No" whilst the amino acid derivatives are also identified by the numbers appended to them in the foreging list and are referred to as "Amino Acid Cpd No."

EXAMPLE 1

5 g of N-benzoylvaline (Amino Acid Compound No. 10-45) were weighed out and dispersed in 80 ml of water. A 1N aqueous solution of sodium hydroxide was slowly added to this dispersion, and dissolved the N-benzoylvaline when the pH of the solution reached a value of 7-8. Then, 5 g of (5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid (Carbapenem Compound No. 6) were dissolved in this solution, to give a total volume of 100 ml.

EXAMPLE 2

5 g of N-benzoyl-β-alanine (Amino Acid Compound No. 2-22) were weighed out and dispersed in 40 ml of water. A 1N aqueous solution of sodium hydroxide was slowly added to this dispersion, and dissolved the N-benzoyl-β-alanine when the pH of the solution reached a value of 7-8. Then, 5 g of (5R,6S)-2-[3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid (Carbapenem Compound No. 6) were dissolved in this solution, to give a total volume of 50 ml.

EXAMPLE 3

Similar procedures to those described in Examples 1 and 2 were carried out, using the other penem or carbapenem antibiotic substances and the other acylated amino acid derivatives shown in the following Table, in the amounts shown in that Table.

In this Table, where the amino acid derivatives are not specified as being D-or L-, then they are the DL-form.

ACTIVITY TESTS

The preparation obtained by the procedure described in Example 1 was injected into the ear vein of a rabbit (about 3 kg body weight) in an amount of 3 ml/kg [that is 150 mg/kg of the Carbapenem Compound No.6 + 150 mg/kg of N-benzoylvaline (Amino Acid Compound No. 10-45)]. A preparation which had been obtained by the same procedure as that described in Example 1 but not including the N-benzoylvaline was injected into another rabbit, as a control, in a similar manner to the above.

After one week, the kidneys of both rabbits were excised and examined. A change was observed in the renal tissue of the rabbits to which had been administered the preparation without the N-benzoylvaline, but no such change at all was observed in the renal tissue of rabbits to which had been administered the preparation containing the N-benzoylvaline.

Similar experiments were carried out on other preparations which were prepared from other penem or carbapenem antibiotic substances and other amino acid derivatives. The Table also shows the results of these experiments.

The observed change in the renal tissue of the control rabbits was a degenerative necrosis of the proximal renal tubules in the region of the renal cortex. In the following Table, where the proportion of the total area of this region which exhibited such necrosis was from 0 to 25%, this is shown as + + +. Where the area is less than 50% this is shown as + + and where it is less than 75% this is shown as +. Where different animals within each test group exhibited different responses, this is shown as e.g. + + + -+ + or + + -+.

It should be noted that, whenever penem or carbapenem antibiotic substances which were not combined with amino acid derivatives were administered, a change in the renal tissue was observed. Hence, all of the experiments carried out (even where the effect is only "+") demonstrated a significant protective effect of the amino acid derivative.

Table

(Carba)-Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
6	150	1-5	150	+
6	150	1-8	150	++
6	150	1-10	150	+
6	150	1-11	150	++
6	150	1-12	150	+
6	150	2-3	150	++
6	150	2-4	150	++
6	150	2-5	150	+++
6	250	2-6	250	+++
6	150	2-7	150	+++
6	150	2-10	150	++
6	150	2-11	150	++
6	150	2-13	150	++
6	150	2-14	150	++
6	150	2-15	150	++

Table (cont)

(Carba)-penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
6	250	2-18	250	+++
6	150	2-22	150	+++
6	200	2-22	200	+++
6	300	2-22	300	+++
6	300	2-22	150	++
6	400	3-3	400	+++
6	150	3-6	150	+
6	150	3-8	150	+
6	150	3-15	150	+
6	150	4-1	150	+
6	150	4-4	150	+
6	150	4-5	150	++
5	150	4-6	150	+++
6	150	5-3	150	++
6	150	5-11	150	++
6	150	5-14	150	+
6	250	5-18	250	++
6	150	5-33	150	+++
6	150	6-2	150	++
6	150	6-3	150	+++
6	150	6-11	150	++
6	150	7-2	150	+

Table (cont)

(Carba)-Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
6	150	7-3	150	+++
6	150	7-5	150	+++
6	150	7-12	150	++
6	150	7-18	150	++
6	150	8-2	150	+
6	150	8-4	150	+++
6	150	8-8	150	++
6	150	8-10	150	+
6	150	9-3	150	+++
6	150	9-5	150	+
6	150	10-4	150	+++
6	250	10-19	250	++
6	150	10-24	150	+
6	150	10-30	150	+
6	150	10-32	150	+
6	150	10-33	150	+
6	150	10-34	150	++
6	150	10-35	150	++
6	150	10-45	150	+++
6	400	10-45	400	+++
6	400	10-45	200	++
6	150	11-3	150	+++

Table (cont)

(Carba)-Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
6	150	11-6	150	+
6	150	11-7	150	+
6	150	11-8	150	+
6	150	11-24	150	+++
6	150	12-1	150	++
6	150	12-4	150	++
6	150	13-1	150	++
6	150	13-2	150	++
6	150	13-5	150	+++
6	150	13-12	150	+
6	150	14-6	150	+++
6	150	14-7	150	+
6	150	14-8	150	++
6	150	14-9	150	+
6	150	14-11	150	+
6	150	14-14	150	+++
6	150	15-1	150	+
6	150	16-3	150	+++
6	150	17-1	150	++
6	150	17-3	150	+
6	150	17-8	150	+

Table (cont)

(Carba)-Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
6	150	18-2	150	+
6	150	19-2	150	+
6	150	19-3	150	+
6	150	21-4	150	+
6	150	22-6	150	+
6	150	23-3	150	++
6	150	24-2	150	++
6	150	25-2	150	+
6	150	26-1	150	+
6	150	27-3	150	+
6	150	30-9	150	+
6	150	31-5	150	+
6	400	33-4	400	+++
6	150	33-5	150	++
6	150	33-7	150	+
6	150	33-11	150	+++
6	150	33-14	150	++
6	150	33-15	150	+
6	150	33-16	150	+
6	150	33-20	150	++
6	150	34-2	150	+++

Table (cont)

(Carba)-Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
6	150	34-3	150	++
6	150	34-6	150	+
6	150	34-8	150	+
6	150	34-12	150	++
6	150	34-13	150	++
6	150	34-14	150	+++
6	150	35-3	150	+
6	150	36-3	150	++
6	150	37-3	150	++
6	150	39-2	150	++
6	150	41-2	150	+
6	150	41-4	150	++
6	150	41-7	150	+
6	150	42-2	150	++
6	150	43-1	150	+
6	150	43-3	150	+++
6	150	43-5	150	+
6	150	43-7	150	++
6	150	43-8	150	++
6	150	44-3	150	++
6	150	45-5	150	+

Table (cont)

(Carba)-Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
6	150	46-1	150	++
6	150	47-3	150	++
6	150	48-2	150	+
6	150	48-5	150	++
6	150	48-9	150	+
6	150	49-2	150	+
6	150	49-7	150	+
6	400	50-5	400	+++
6	150	50-6	150	+++
6	150	50-7	150	+++
6	150	50-10	150	++
6	150	50-12	150	++
6	150	51-1	150	++
6	150	52-6	150	++
6	150	53-1	150	++
6	150	54-1	150	++
6	150	55-3	150	++
6	150	56-3	150	++
6	150	57-3	150	+++
6	150	57-4	150	++
6	150	57-6	150	+

Table (cont)

(Carba)-Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
6	150	57-7	150	+
6	150	58-1	150	+
6	150	58-3	150	++
6	150	58-6	150	+
6	150	58-9	150	+
6	150	59-1	150	+++
6	150	59-4	150	++
6	150	59-7	150	++
6	150	60-2	150	+
6	150	60-6	150	+
6	150	61-2	150	++
1	150	2-22	150	++
1	150	3-3	150	++
1	250	5-11	250	+++
1	150	5-18	150	+++
1	150	10-45	150	++
1	150	14-6	150	+++
1	150	33-4	150	+++
1	150	34-10	150	++
1	150	50-5	150	++
2	150	4-6	150	+++

Table (cont)

(Carba)-Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
2	150	5-11	150	+++
2	150	7-14	150	+++
2	250	9-3	250	+++
2	150	10-23	150	++
2	150	33-15	150	++
2	250	50-5	250	++
2	150	50-23	150	++
3	150	5-11	150	+++
3	250	10-29	250	+++
3	250	13-5	250	++
3	150	13-13	150	++
3	150	33-20	150	++
3	250	34-2	250	++
3	150	50-12	150	++
7	150	2-22	150	+++
7	250	5-11	250	++
7	150	10-45	150	+++
7	150	14-1	150	+++
7	150	50-6	150	+++
8	150	2-22	150	++
8	150	6-11	150	+-++

Table (cont)

(Carba)-Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
8	250	50-5	250	++-+++
9	150	33-6	150	+
9	250	50-5	250	++
10	150	13-5	150	++
10	150	18-6	150	+
11	150	2-22	150	++
15	150	10-45	150	+++
19	150	L-10-45	150	++
22	250	33-4	250	++
22	150	34-15	150	+-++
23	150	2-22	150	+++
24	150	2-22	150	+++
24	150	10-45	150	+++
24	150	D-10-45	150	+++
24	150	L-10-45	150	+++
24	150	18-5	150	+
25	150	9-3	150	++

Table (cont)

(Carba)-Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
28	150	3-18	150	+
28	150	33-21	150	+++
32	150	2-22	150	++
38	150	2-22	150	+++
39	150	10-45	150	++
40	150	2-22	150	+++
66	250	3-3	250	++
67	150	5-19	150	++
67	150	12-4	150	+-++
71	250	2-18	250	+++
71	250	5-21	250	++
73	150	11-27	150	+
73	150	34-10	150	++
75	150	14-6	150	++
75	150	33-9	150	++

Claims

1. A composition comprising:
a penem or carbapenem antibiotic; and
a pharmaceutically acceptable N-acylated derivative of an amino acid wherein the amino group and the carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof, provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.

2. A composition as claimed in Claim 1, wherein said amino acid is a compound of formula (II):
H_2N-X-COOH (II)
wherein X represents a C_1-C_{10} alkylene group or a C_1-C_{10} alkylene group having at least one substituent selected from hydroxy groups, C_1-C_4 alkoxy groups, C_6-C_{14} aryloxy groups, substituted C_6-C_{14} aryloxy groups, C_7-C_9 aralkyloxy groups, substituted C_7-C_9 aralkyloxy groups, mercapto groups, C_1-C_4 alkylthio groups, C_6-C_{14} arylthio groups, substituted C_6-C_{14} arylthio groups, C_7-C_9 aralkylthio groups, substituted C_7-C_9

aralkylthio groups, C_2-C_5 carboxyalkylthio groups, amino groups, amino groups having one or two substituents selected from
C_1-C_4 alkyl groups, C_6-C_{14} aryl groups, substituted C_6-C_{14} aryl groups, C_7-C_9 aralkyl groups, substituted C_7-C_9 aralkyl groups and carboxylic acyl groups,
C_6-C_{14} aryl groups, substituted C_6-C_{14} aryl groups, carboxy groups, amidino groups, sulpho groups, C_1-C_4 alkylsulphinyl groups, C_1-C_4
alkylsulphonyl groups and heterocyclic groups having from 5 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said substituted aryloxy, arylthio, aralkylthio, aryl and aralkyl groups having at least one substituent selected from C_1-C_4 alkyl groups, hydroxy groups amino groups and C_1-C_4 alkoxy groups,
or a pharmaceutically acceptable salt thereof.

3. A composition as claimed in Claim 2, wherein X represents a C_1-C_5 alkylene group which is unsubstituted or has one or two substituents selected from: hydroxy grtoups; C_1-C_4 alkoxy groups; aryloxy groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; C_7-C_9 aralkyloxy groups, wherein the aryl moiety is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; mercapto groups; C_1-C_4 alkylthio groups; arylthio groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; C_7-C_9 aralkylthio groups wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups;
carboxyalkylthio groups in which the alkyl part has from 1 to 4 carbon atoms; amino groups; amino groups having one or two C_1-C_4 alkyl substituents; amino groups having one or two aryl substituents in which the aryl ring has from 6 to 14 ring carbon atoms and is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; amino groups having one or two C_7-C_9 aralkyl substituents in which the aryl part is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; amino groups having one or two carboxylic acyl substituents; aryl groups having from 6 to 14 ring carbon atoms and being unsubstituted or having from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms.

4. A composition as claimed in Claim 2, wherein X represents a C_1-C_5 alkylene group which is unsubstituted or has 1 or 2 substituents selected from: hydroxy groups; C_1-C_4 alkoxy groups; mercapto groups; C_1-C_4 alkylthio groups; amino groups; amino groups haiving one or two C_1-C_4 alkyl substituents; amino groups having one or two carboxylic acyl substituents; aryl groups having from 6 to 14 carbon atoms wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen hetero-atoms.

5. A composition as claimed in any; one of Claims 1 to 4, wherein the N-acyl group is: a C_1-C_{18} alkanoyl group; a C_3-C_8 alkenoyl group; a C_3-C_8 alkynoyl group; an aromatic acyl group wherein the aryl part is C_6-C_{14} carbocyclic aryl and is unsubstituted or has from 1 to 5 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, C_1-C_4 alkoxy groups, amino groups, sulpho grtoups and halogen atoms; a cycloalkanecarbonyl group where the cycloalkane part is C_3-C_8 and is unsubstituted or has at least one substituent selected from C_1-C_4 alkyl groups and phenyl groups; an araliphatic acyl group in which the aryl ring is a carbocyclic ring having from 6 to 14 carbon atoms and which is unsubstituted or has from 1 to 5 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, C_1-C_4 alkoxy groups, amino groups, sulpho groups and halogen atoms, and in which the alkyl moiety has from 1 to 4 carbon atoms; a heterocyclic acyl group which has a saturated or unsaturated ring system, the rings having 5 or 6 ring atoms, of which from 1 to 3 are nitrogen and/or sulphur and/or oxygen hetero-atoms and the ring being unsubstituted or having from 1 to 3 substituents selected from C_1-C_4 alkyl groups and hydroxy groups; a C_2-C_7 alkoxycarbonyl group; an aralkyloxycarbonyl group where the aralkyl part has from 7 to 9 carbon atoms and is unsubstituted or has from 1 to 5 substituents selected from amino groups, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups and hydroxy groups; or an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N -acylation of the amino group with at least one of the above-mentioned acyl groups.

6. A composition as claimed in any one of Claims 1 to 4, wherein the N-acyl group is: a saturated aliphatic acyl group having from 1 to 8 carbon atoms; an aromatic acyl group in which the aryl moiety has from 6 to 10 ring carbon atoms and is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups; an alicyclic acyl group in which the cycloalkane ring has from 3 to 6 carbon atoms; an araliphatic acyl group in which the aryl ring has from 6 to 10 ring carbon atoms and the alkyl group has from 1 t o 4 carbon atoms, the aryl ring being unsubstituted or having from 1 to 3 substituents selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups; a heterocyclic acyl group in which the heterocyclic ring is saturated or unsaturated and has 5 or 6 ring atoms of which one is a nitrogen, sulphur or oxygen hetero-atom; an alkoxycarbonyl group having a total of from 2 to 7 carbon atoms; an aralkyloxycarbonyl group in which the aralkyl moiety has from 7 to 9 carbon atoms and the aryl ring is unsubstituted or has from 1 to 3 substituents selected C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups; or an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups.

7. A composition as claimed in any; one of Claims 1 to 4, wherein the N -acyl group is: an aromatic acyl group in which the aryl ring has from 6 to 10 ring atoms and which is unsubstituted or has a single substituent selected from C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups, hydroxy groups and amino groups; an alicyclic acyl group in which the cycloalkane moiety has from 3 to 6 carbon atoms; a phenylaliphatic acyl group in which the phenyl group is unsubstituted or has a single C_1-C_4 alkyl substituent, and in which the alkyl part has from 1 to 4 carbon atoms; an alkoxycarbonyl group having a total of from 4 to 6 carbon atoms; an aralkyloxycarbonyl group in which the aralkyl part has from 7 to 9 carbon atoms and has 0 to 1 substituent selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups; or an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups.

8. A composition as claimed in any one of Claims 1 to 4 wherein the N-acyl group is an acetyl, benzoyl, cyhclohexanecarbonyl, cyclopropanecarbonyl, hexanoyl, isobutyryl, crotonoyl, ethoxycarbonyl, 4-hydroxybenzoyl, anisoyl, 4-aminobenzoyl, naphthoyl, toluoyl, benzyloxycarbonyl or 4-methoxybenzyloxycarbonyl group.

9. A composition as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is glycine, β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, 8-aminooctanoic acid, alanine, 2-aminobutyric acid, norvaline valine, leucine, isoleucine, norleucine, tyrosine, O-methyltyrosine, aspartic acid, glutamic acid, 4-carboxyglutamic acid, 3-methylaspartic acid, 2-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid, 3-hydroxyaspartic acid, 3-hydroxyglutamic acid, 2,3-diaminopropionic acid, 2,4-diaminobutyric acid, 5-hydroxylysine, arginine, N^{δ},N^{δ}-dimethylornithine, N^{ϵ}-methyllysine, cysteine, methionine, ethionine,S-carboxymethylcysteine, S-benzylcysteine, methionine S-oxide, ethionine S-oxide, methionine S,S-dioxide, cysteic acid, serine, O-methylserine, threonine, O-methylthreonine, homothreonine, ethoxinine, 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, tryptophan, 2-methylalanine, 2-methylserine, 2-hydroxyisoleucine, 2-methylmethionine, 2-ethyl-2-phenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid, 3-amino-3-phenylpropionic acid, 3-amino-2-hydroxypropionic acid or 4-amino-3-hydroxybutyric acid.

10. A composition as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is glycine, β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, 8-aminooctanoic acid, alanine, norvaline, valine, leucine, isoleucine, norleucine, N^{δ},N^{δ}-dimethylornithine, methionine, ethionine, O-methylserine, O-methylthreonine, ethoxinine, 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, 2-methylalanine, 2-methylserine, 2-hydroxyisoleucine, 2-ethylphenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid or 3-amino-3-phenylpropionic acid.

11. A composition as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, alanine, valine, leucine, norleucine, methionine, histidine or glycine.

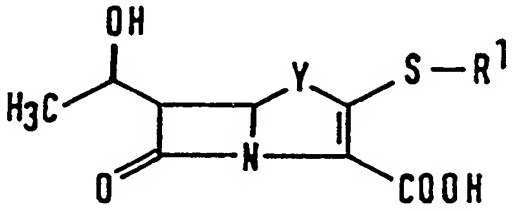
12. A composition as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is leucylglycine, glycyl-β-alanine, glycylalanine, valylalanine, leucylalanine, glycylvaline, alanylvaline, leucylvaline, valylleucine, phenylalanylleucine, histidylleucine, glycylphenylalanine, alanylphenylalanine, leucylphenylalanine, glycylmethionine, valylmethionine, glycylhistidine, alanylvalylglycine, glycylalanylvaline, glycylphenylalanylleucine or glycylglycylhistidine.

13. A composition as claimed in Claim 1, wherein said N-acylated amino acid is:

N-(o -toluoyl)-β-alanine
N-(4-methoxybenzoyl)-β-alanine
N-(3-hydroxy-2-naphthoyl)-β-alanine
N-benzoylglycyl-β-alanine

N-benzoyl-β-alanine
N-benzoyl-5-aminovaleric acid
N-benzoyl-6-aminohexanoic acid
N-cyclohexanecarbonyl-6-aminohexanoic acid
N-(N -methylnicotinoyl)-6-aminohexanoic acid
N-benzoyl-8-aminooctanoic acid
N-benzoylalanine
N-(1-naphthoyl)alanine
N-benzoylvalylalanine
N-benzoyl-2-aminobutyric acid
N-benzoylnorvaline
N-valerylvaline
N-benzoylalanylvaline
N-benzoylvaline
N-benzoylleucine
N-benzoylglycylphenylalanylleucine
N-benzoylnorleucine
N-benzoylglycylphenylalanine
N-benzoylalanylphenylalanine
N-cyclohexanecarbonylleucylphenylalanine
N-benzoyl-O-methyltyrosine
N-benzoylmethionine
N-phenylacetylmethionine
N-benzoylvalylmethionine
N-benzoylethionine
N-(4-methoxybenzyloxycarbonyl)ethionine
N-benzoylthreonine
N-benzoylhistidine
N-(p-toluoyl)histidine
N-(4-methoxybenzoyl)histidine
N-(4-methoxybenzoyl)-3-aminobutyric acid
or
N-butyryl-3-amino-3-phenylpropionic acid.

14. A composition as claimed in any one of the preceding Claims, wherein said antibiotic is a compound of formula (I):



(I)

Y represents a sulphur atom, a methylene group or a methylene group having 1 or 2 methyl and/or methoxy substituents; and

R' represents a C_1-C_6 alkyl group, a C_1-C_6 alkyl group having at least one of substituents (i) or a heterocyclic group having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms where said heterocyclic group is unsubstituted or has at least one of substituents (ii);

substituents (i):

halogen atoms, amino groups, amino groups having at least one of substituents (iii), C_1-C_4 alkylideneamino groups, C_1-C_4 aminoalkylideneamino groups, amindino groups, amidino groups having from 1 to 3 of substituents (iii), heterocyclic groups having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms wherein said heterocyclic group is unsubstituted or has at least one of substituents (ii), imino groups, cyano groups, carbamoyl groups and carbamoyl groups having at least one substituent selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups;

substituents (ii):
C_1-C_6 alkanimidoyl groups, C_1-C_6 alkyl groups, alkoxyalkyl groups where the alkoxy and alkyl parts are each C_1-C_4, carbamoyl groups, carbamoyl groups having at least one substituent selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups, C_1-C_4 haloalkyl groups, heterocyclic acylimidoyl groups where the heterocyclic part has from 5 to 9 ring atoms of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur heteroatoms, amidino groups, amidino groups having from 1 to 3 of substituents (iii), imino groups, oxygen atoms, C_1-C_6 alkanoyl groups, C_1-C_6 alkanesulphonyl groups, C_1-C_6 alkanesulphinyl groups, hydroximino groups, C_1-C_4 alkoximino groups, carbamoyloxy groups, carbamoyloxy groups having at least one substituent selected from C_1-C_4 alkyl gorups and C_1-C_4 alkoxy groups, carbamoyloxylalkyl groups where the alkyl part is C_1-C_4 and the carbamoyl part is unsubstituted or has at least one substituent selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups and C_1-C_4 iminoalkyl groups;
substituents (iii):
C_1-C_6 alkyl groups, C_2-C_6 alkenyl groups, C_2-C_6 alkynyl groups, oxygen atoms and said alkyl, alkenyl and alkynyl groups having at least one substituent selected from halogen atoms, carbamoyloxy groups and carbamoyloxy groups having at least one substituent selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups;
and pharmaceutically acceptable salts thereof.

15. A composition as claimed in Claim 14, wherein Y represents a sulphur atom, a methylene group, or the group CH_3-CH<, CH_3O-CH< or $(CH_3)_2C$<.

16. A composition as claimed in Claim 14 or Claim 15, wherein R^1 represents an ethyl, 2-fluoroethyl, 2-(aminomethyleneamino)ethyl, N',N'-dimethylamidinomethyl, N', N', N^2-trimethylamidinomethyl, 3-pyrrolidinyl, 1-formimidoyl-3-pyrrolidinyl, 1-acetimidoyl-3-pyrrolidinyl, 1-propionimidoyl-3-pyrrolidinyl, 2-methyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 2-methoxymethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 3-azetidinyl, 1-acetimidoyl-3-azetidinyl, N'-methyl-N'-(2-propynyl)amidinomethyl, N'-(2-fluoroethyl)-N'-methylamidinomethyl, N'-(3-fluoropropyl)-N'-methylamidinomethyl, N'-methyl-N'-(2,2,2-trifluoroethyl)-amidinomethyl,1-(3-azetidinyl)ethyl, 1-(1-acetimidoyl-3-azetidinyl)ethyl, 1,4,5,6-tetrahydro-2-pyrimidinylmethyl, 1-(4,5-dihydro-2-thiazolyl)ethyl, 5-carbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-carbamoyl-3-pyrrolidinyl, 2-chloromethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 1-butyrimidoyl-3-pyrrolidinyl, 1-nicotinimidoyl-3-pyrrolidinyl, N',N'-diallylamidinomethyl, N'-methyl-N'-(2-propynyl)amidino, N'-(2-fluoroethyl)-N'-methylamidino, N'-(3-fluoropropyl)-N'-methylamidino, N'-methyl-N'-(2,2,2-trifluoroethyl)amidino, N'-allyl-N'-methylamidinomethyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 2-cyano-1-methylethyl, 2-aminoethyl, 1-carbamoylethyl, 2-(1-aminoethylideneamino)ethyl, 1-amidino-3-pyrrolidinyl, 2-methyl-1,3-diazabicyclo-[3.3.0]oct-2-en-7-yl, 2-methoxymethyl-1,3-diazabicyclo[3.3.0]oct-2-en-7-yl, 5-imino-2-pyrrolidinyl, 2-imino-5-piperidinyl, 1-acetimidoyl-5-methylcarbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-methoxycarbamoyl-3-pyrrolidinyl, 2-imino-2-(S-oxothiomorpholino)ethyl, 2-imino-2-(1,1-dioxo-1,3-thiazolidin-3-yl)ethyl, 2-imino-2-(S,S-dioxothiomorpholino)ethyl, 2-imino-2-(3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-acetyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methanesulphonyl-3-oxo-1-piperazinyl)ethyl, N'-(2-carbamoyloxyethyl)-N'-methylamidinomethyl, 2-(3-hydroximino-1-pyrrolidinyl)2-iminoethyl, 2-imino-2-(3-methoximino-1-pyrrolidinyl)-ethyl, 2-(4-hydroximinopiperidino)-2-iminoethyl, 2-imino-2-(4-methoximinopiperidino)ethyl, 2-(3-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-imino-2-(3-oxo-1-piperazinyl)ethyl, 2-(3-carbamoylpiperidino)-2-iminoethyl, 2-(3-carbamoyloxypiperidino)-2-iminoethyl, 2-(2-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-(2-carbamoyloxymethyl-1-pyrrolidinyl)-2-iminoethyl, 2-(4-carbamoyloxypiperidino)-2-iminoethyl, 2-(4-formyl-1-piperazinyl)-2-iminoethyl, 2-(4-acetyl-1-piperazinyl)-2-iminoethyl, 1-formyl-3-azetidinyl, 1-iminomethyl-3-azetidinyl, 1-methyl-4-piperidyl, 1-acetimidoyl-4-piperidyl or 1-acetyl-3-pyrrolidinyl group.

17. A composition as claimed in Claim 14, wherein said antibiotic is:
(5R,6S)-2-{2-[(aminomethylene)amino]ethylthio}-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid
(5R,6S)-2[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S)-methyl-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(R)-methyl-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S)-methyl-2-carbapenem-3-carboxylic acid
or
(5R,6S)-2-[(3S)-1-acetimidoyl-5(S)-carbamoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid.

18. A composition as claimed in any one of the preceding Claims, wherein the weight ratio of said N-acylated amino acid to said antibiotic is from 0.1:1 to 4:1.

19. A packaged pharmaceutical preparation comprising:

(a) in one part, a penem or carbapenem antibiotic; and

(b) in another part, a pharmaceutically acceptable N-acylated derivative of an amino acid wherein the amino group and the carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof, provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.

20. A preparation as claimed in Claim 19, wherein said N-acylated amino acid is as defined in any one of Claims 2 to 13.

21. A preparation as claimed in Claim 19 or Claim 20, wherein said antibiotic is as defined in any one of Claims 14 to 17.

22. The use for the manufacture of a medicament for the treatment of bacterial infections of:

(a) a penem or carbapenem antibiotic;

in association with:

(b) a pharmaceutically acceptable N -acylated derivative of an amino acid wherein the amino group and the carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof, provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.

23. The use as claimed in Claim 22, wherein said N-acylated amino acid is as defined in any one of Claims 2 to 13.

24. The use as claimed in Claim 22 or Claim 23, wherein said antibiotic is as defined in any one of Claims 14 to 17.

Claims for the following Contracting States : AT, ES:

1. A method of making a pharmaceutical composition by mixing:

a penem or carbapenem antibiotic; and

a pharmaceutically acceptable N-acylated derivative of an amino acid wherein the amino group and the carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof, provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.

2. A method as claimed in Claim 1, wherein said amino acid is a compound of formula (II):

H_2N-X-COOH (II)

wherein X represents a C_1-C_{10} alkylene group or a C_1-C_{10} alkylene group having at least one substituent selected from hydroxy groups, C_1-C_4 alkoxy groups, C_6-C_{14} aryloxy groups, substituted C_6-C_{14} aryloxy groups, C_7-C_9 aralkyloxy groups, substituted C_7-C_9 aralkyloxy groups, mercapto groups, C_1-C_4 alkylthio groups, C_6-C_{14} arylthio groups, substituted C_6-C_{14} arylthio groups, C_7-C_9 aralkylthio groups, substituted C_7-C_9 aralkylthiio groups, C_2-C_5 carboxyalkylthio groups, amino groups, amino groups having one or two substituents selected from

C_1-C_4 alkyl groups, C_6-C_{14} aryl groups, substituted C_6-C_{14} aryl groups, C_7-C_9 aralkyl groups, substituted C_7-C_9 aralkyl groups and carboxylic acyl groups,

C_6-C_{14} aryl groups, substituted C_6-C_{14} aryl groups, carboxy groups, amidino groups, sulpho groups, C_1-C_4 alkylsulphinyl groups, C_1-C_4 alkylsulphonyl groups and heterocyclic groups having from 5 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said substituted aryloxy, aralkyloxy, arylthiio, aralkylthio, aryl and aralkyl groups having at least one substituent selected from C_1-C_4 alkyl groups, hydroxy; groups, amino groups and C_1-C_4 alkoxy groups,

or a pharmaceutically acceptable salt thereof.

3. A method as claimed in Claim 2, wherein X represents a C_1-C_5 alkylene group which is unsubstituted or has one or two substituents selected from: hydroxy groups; C_1-C_4 alkoxy groups; aryloxy groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; C_7-C_9 aralkyloxy groups, wherein the aryl moiety is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; mercapto groups; C_1-C_4 alkylthio groups; arylthio groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; C_7-C_9 aralkylthio groups wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; carboxyalkylthio groups in which the alkyl part has from 1 to 4 carbon atoms; amino groups; amino groups having one or two C_1-C_4 alkyl substituents; amino groups having one or two aryl substituents in which the aryl ring has

from 6 to 14 ring carbon atoms and is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; amino groups having one or two C_7-C_9 aralkyl substituents in which the aryl part is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; amino groups having one or two carboxylic acyl substituents; aryl groups having from 6 to 14 ring carbon atoms and being unsubstituted or having from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms.

4. A method as claimed in Claim 2, wherein X represents a C_1-C_3 alkylene group which is unsubstituted or has 1 or 2 substituents selected from: hydroxy groups; C_1-C_4 alkoxy groups; mercapto groups; C_1-C_4 alkylthio groups; amino groups; amino groups having one or two C_1-C_4 alkyl substituents; amino groups having one or two carboxylic acyl substituents; aryl groups having from 6 to 14 carbon atoms wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, amino groups and C_1-C_4 alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen hetero-atoms.

5. A method as claimed in any one of Claims 1 to 4, wherein the N-acyl group is: a C_1-C_{18} alkanoyl group; a C_3-C_8 alkenoyl group; a C_3-C_8 alkynoyl group; an aromatic acyl group wherein the aryl part is C_6-C_{14} carbocyclic aryl and is unsubstituted or has from 1 to 5 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, C_1-C_4 alkoxy groups, amino groups, sulpho groups and halogen atoms; a cycloalkanecarbonyl group where the cycloalkane part is C_3-C_8 and is unsubstituted or has at least one substituent selected from C_1-C_4 alkyl groups and phenyl groups; an araliphatic acyl group in which the aryl ring is a carbocyclic ring having from 6 to 14 carbon atoms and which is unsubstituted or has from 1 to 5 substituents selected from C_1-C_4 alkyl groups, hydroxy groups, C_1-C_4 alkoxy groups, amino groups, sulpho groups and halogen atoms, and in which the alkyl moiety has from 1 to 4 carbon atoms; a heterocyclic acyl group which has a saturated or unsaturated ring system, the rings having 5 or 6 ring atoms, of which from 1 to 3 are nitrogen and/or sulphur and/or oxygen hetero-atoms and the ring being unsubstituted or having from 1 to 3 substituents selected from C_1-C_4 alkyl groups and hydroxy groups; a C_2-C_7 alkoxycarbonyl groups; an aralkyloxycarbonyl group where the aralkyl part has from 7 to 9 carbon atoms and is unsubstituted or has from 1 to 5 substituents selected from amino groups, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups and hydroxy groups; or an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups.

6. A method as claimed in any one of Claims 1 to 4, wherein the N-acyl group is: a saturated aliphatic acyl group having from 1 to 8 carbon atoms; an aromatic acyl group in which the aryl moiety has from 6 to 10 ring carbon atoms and is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups; an alicyclic acyl group in which the cycloalkane ring has from 3 to 6 carbon atoms; an araliphatic acyl group in which the aryl ring has from 6 to 10 ring carbon atoms and the alkyl group has from 1 to 4 carbon atoms, the aryl ring being unsubstituted or having from 1 to 3 substituents selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups; a heterocyclic acyl group in which the heterocyclic ring is saturated or unsaturated and has 5 or 6 ring atoms of which one is a nitrogen, sulphur or oxygen hetero-atom; an alkoxycarbonyl group having a total of from 2 to 7 carbon atoms; an aralkyloxycarbonyl group in which the aralkyl moiety has from 7 to 9 carbon atoms and the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups; or an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups.

7. A method as claimed in any one of Claims 1 to 4, wherein the N-acyl group is: an aromatic acyl group in which the aryl ring has from 6 to 10 ring atoms and which is unsubstituted or has a single substituent selected from C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups, hydroxy groups and amino groups; an alicyclic acyl group in which the cycloalkane moiety has from 3 to 6 carbon atoms; a phenylaliphatic acyl group in which the phenyl group is unsubstituted or has a single C_1-C_4 alkyl substituent, and in which the alkyl part has from 1 to 4 carbon atoms; an alkoxycarbonyl group having a total of from 4 to 6 carbon atoms; an aralkyloxycarbonyl group in which the aralkyl part has from 7 to 9 carbon atoms and has 0 or 1 substituent selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups; or an acyl group derived from am amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups.

8. A method as claimed in any one of Claims 1 to 4, wherein the N-acyl group is an acetyl, benzoyl, cyclohexanecarbonyl, cyclopropanecarbonyl, hexanoyl, isobutyryl, crotonoyl ethoxycarbonyl, 4-hydroxybenzoyl, anisoyl, 4-aminobenzoyl, naphthoyl, toluoyl, benzyloxycarbonyl or 4-methoxybenzyloxycarbonyl group.

9. A method as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is glycine, β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, 8-aminooctanoic acid, alanine, 2-aminobutyric acid, norvaline, valine, leucine, isoleucine, norleucine, tyrosine, O-methyltyrosine, aspartic acid, glutamic acid, 4-carboxyglutamic acid, 3-methylaspartic acid, 2-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid, 3-hydroxyaspartic acid, 3-hydroxyglutamic acid, 2,3-diaminopropionic acid 2,4-diaminobutyric acid, 5-hydroxylysine, arginine, N^{δ},N^{δ}-dimethylhornithine, N^{ϵ}-methyllysine, cysteine, methionine, ethionine, S-carboxymethylcysteine, S-benzylcysteine, methionine S-oxide, ethionine S-oxide, methionine S,S-dioxide, cysteic acid, serine, O -methylserine, threonine, O-methylthreonine, homothreonine, ethoxinine, 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, tryptophan, 2-methylalanine, 2-methylserine 2-hydroxyisoleucine, 2-methylmethionine, 2-ethyl-2-phenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid, 3-amino-3-phenylpropionic acid,
3-amino-2-hydroxypropionic acid or
4-amino-3-hydroxybutyric acid.

10. A method as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is glycine, β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, 8-aminooctanoic acid, alanine, norvaline, valine, leucine, isoleucine, norleucine, N^{δ},N^{δ}-dimethylornithine, methionine, ethionine, O -methylserine, O-methylthreonine, ethoxinine, 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, 2-methylalanine, 2-methylserine, 2-hydroxyisoleucine, 2-ethylphenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid or 3-amino-3-phenylpropionic acid.

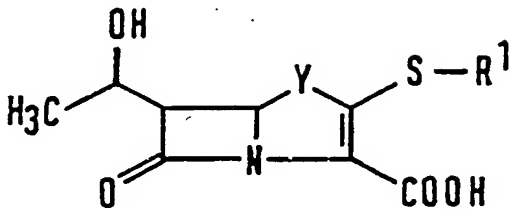
11. A method as claimed in any one of Claims 1 and 5 to 8, wherein waid amino acid is β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, alanine valine leucine, norleucine methionine, histidine or glycine.

12. A method as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is leucylglycine, glycyl-β-alanine, glycylalanine, valylalanine, leucylalanine, glycylvaline, alanylvaline, leucylvaline, valylleucine phenylalanylleucine, histidylleucine, glycylphenylalanine, alanylphenylalanine, leucylphenylalanine, glycylmethionine valylmethionine, glycylhistidine, alanylvalylglycine, glycylalanylvaline, glycylphenylalanylleucine or glycylglycylhistidine.

13. A method as claimed in Claim 1, wherein said N-acylated amino acid is:
N-(p-toluoyl)-β-alanine
N-(4-methoxybenzoyl)-β-alanine
N-(3-hydroxy-2-naphthoyl)-β-alanine
N-benzoylglycyl-β-alanine
N-benzoyl-β-alanine
N-benzoyl-5-aminovaleric acid
N-benzoyl-6-aminohexanoic acid
N-cyclohexanecarbonyl-6-aminohexanoic acid
N-(N -methylnicotinoyl)-6-aminohexanoic acid
N-benzoyl-8-aminooctanoic acid
N-benzoylalanine
N-(1-naphthoyl)alanine
N-benzoylvalylalanine
N-benzoyl-2-aminobutyric acid
N-benzoylnorvaline
N-valerylvaline
N-benzoylalanylvaline
N-benzoylvaline
N-benzoylleucine
N-benzoylglycylphenylalanylleucine
N-benzoylnorleucine
N-benzoylglycylphenylalanine
N-benzoylalanylphenylalanine
N-cyclohexanecarbonylleucylphenylalanine
N-benzoyl-O-methyltyrosine
N-benzoylmethionine
N-phenylacetylmethionine
N-benzoylvalylmethionine
N-benzoylethionine
N-(4-methoxybenzyloxycarbonyl)ethionine

N-benzoylthreonine
N-benzoylhistidine
N-(p-toluoyl)histidine
N-(4-methoxybenzoyl)histidine
N-(4-methoxybenzoyl)-3-aminobutyric acid
or
N-butyryl-3-amino-3-phenylpropionic acid.

14. A method as claimed in any one of the preceding Claims, wherein said antibiotic is a compound of formula (I):



(I)

in which:
Y represents a sulphur atom, a methylene group or a methylene group having 1 or 2 methyl and/or methoxy substituents; and
R^1 represents a C_1-C_6 alkyl group, a C_1-C_6 alkyl group having at least one of substituents (i) or a heterocyclic group having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms where said heterocyclic group is unsubstituted or has at least one of substituents (ii);
substituents (i):
halogen atoms, amino groups, amino groups having at least one of substituents (iii), C_1-C_4 alkylideneamino groups, C_1-C_4 aminoalkylideneamino groups, amidino groups, amidino groups having from 1 to 3 of substituents (iii), heterocyclic groups having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms wherein said heterocyclic group is unsubstituted or has at least one of substituents (ii), imino groups, cyano groups, carbamoyl groups and carbamoyl groups having at least one substituent selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups;
substituents (ii):
C_1-C_6 alkanimidoyl groups, C_1-C_6 alkyl groups, alkoxyalkyl groups where the alkoxy and alkyl parts are each C_1-C_4, carbamoyl groups, carbamoyl groups having at least one substituent selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups, C_1-C_4 haloalkyl groups, heterocyclic acylimidoyl groups where the heterocyclic part has from 5 to 9 ring atoms of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms, amidino groups, amidino groups having from 1 to 3 of substituents (iii), amino groups, oxygen atoms, C_1-C_6 alkanoyl groups, C_1-C_6 alkanesulphonyl groups, C_1-C_6 alkanesulphinyl groups, hydroximino groups, C_1-C_4 alkoximino groups, carbamoyloxy groups, carbamoyloxy groups having at least one substituent selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups, carbamoyloxyalkyl groups where the alkyl part is C_1-C_4 and the carbamoyl part is unsubstituted or has at least one substituent selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups and C_1-C_4 iminoalkyl groups;
substituents (iii):
C_1-C_6 alkyl groups, C_2-C_6 alkenyl groups, C_2-C_6 alkynyl groups, oxygen atoms and said alkyl, alkenyl and alkynyl groups having at least one substituent selected from halogen atoms, carbamoyloxy groups and carbamoyloxy groups having at least one substituent selected from C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups;
and pharmaceutically acceptable salts thereof.

15. A method as claimed in Claim 14, wherein Y represents a sulphur atom, a methylene group, or the group CH_3-CH<, CH_3O-CH< or $(CH_3)_2$C<.

16. A method as claimed in Claim 14 or Claim 15, wherein R_1 represents an ethyl, 2-fluoroethyl, 2-(aminomethyleneamino)ethyl, N',N'-dimethylamidinomethyl, N',N',N^2-trimethylamidinomethyl, 3-pyrrolidinyl, 1-formimidoyl-3-pyrrolidinyl, 1-acetimidoyl-3-pyrrolidinyl, 1-propionimidoyl-3-pyrrolidinyl, 2-methyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 2-methoxymethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 3-azetidinyl, 1-acetimidoyl-3-azetidinyl, N'-methyl-N'-(2-propynyl)amidinomethyl, N'-(2-fluoroethyl)-N'-methylamidinomethyl, N'-(3-fluoropropyl)-N'-methylamidinomethyl, N'-methyl-N'-(2,2,2-trifluoroethyl)amidinomethyl, 1-(3-azetidinyl)ethyl,

1-(1-acetimidoyl-3-azetidinyl)ethyl, 1,4,5,6-tetrahydro-2-pyrimidinylmethyl, 1-(4,5-dihydro-2-thiazolyl)ethyl, 5-carbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-carbamoyl-3-pyrrolidinyl, 2-chloromethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 1-butyrimidoyl-3-pyrrolidinyl, 1-nicotinimidoyl-3-pyrrolidinyl, N',N'-diallylamidinomethyl, N'-methyl-N'-(2-propynyl)amidino, N'-(2-fluoroethyl)-N'-methylamidino, N'-(3-fluoropropyl)-N'-methylamidino, N'-methyl-N'-(2,2,2-trifluoroethyl)amidino, N'-allyl-N'-methylamidinomethyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 2-cyano-1-methylethyl, 2-aminoethyl, 1-carbamoylethyl, 2-(1-aminoethylideneamino)ethyl, 1-amidino-3-pyrrolidinyl, 2-methyl-1-3-diazabicyclo-[3.3.0]oct-2-en-7-yl, 2-methoxymethyl-1,3-diazabicyclo-[3.3.0]oct-2-en-7-yl, 5-imino-2-pyrrolidinyl, 2-imino-5-piperidinyl, 1-acetimidoyl-5-methylcarbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-methoxycarbamoyl-3-pyrrolidinyl, 2-imino-2-(S-oxothiomorpholino)ethyl, 2-imino-2-(1,1-dioxo-1,3-thiazolidin-3-yl)ethyl, 2-imino-2-(S,S-dioxothiomorpholino)ethyl, 2-imino-2-(3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-acetyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methanesulphonyl-3-oxo-1-piperazinyl)ethyl, N'-(2-carbamoyloxyethyl)N'-methylamidinomethyl, 2-(3-hydroximino-1-pyrrolidinyl)-2-iminoethyl, 2-imino-2-(3-methoximino-1-pyrrolidinyl)ethyl, 2-(4-hydroximinopiperidino)-2-iminoethyl, 2-imino-2-(4-methoximinopiperidino)ethyl, 2-(3-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-imino-2-(3-oxo-1-piperazinyl)ethyl, 2-(3-carbamoylpiperidino)-2-iminoethyl, 2-(3-carbamoyloxypiperidino)-2-iminoethyl, 2-(2-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-(2-carbamoyloxymethyl-1-pyrrolidinyl)-2-iminoethyl, 2-(4-carbamoyloxypiperidino)-2-iminoethyl, 2-(4-formyl-1-piperazinyl)-2-iminoethyl, 2-(4-acetyl-1-piperazinyl)-2-iminoethyl, 1-formyl-3-azetidinyl, 1-iminomethyl-3-azetidinyl, 1-methyl-4-piperidyl, 1-acetimidoyl-4-piperidyl or 1-acetyl-3-pyrrolidinyl group.

17. A method as claimed in Claim 14, wherein said antibiotic is:
(5R,6S)-2-{2-[(aminomethylene)amino]ethylthio}-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3S-1-acetimidoylpyrrolidin-3-ylthio]-6-[1R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid -
(5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S)-methyl-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(R)-methyl-2-carbapenem-3-carboxylic acid
(5R,6S-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R-hydroxyethyl]-1(S)-methyl-2-carbapenem-3-carboxylic acid
or (5R ,6S)-2-[(3S)-1-acetimidoyl-5(S)-carbamoylpyrrolidin-3-ylthio]-6-[1(R-hydroxyethyl]-2-carbapenem-3-carboxylic acid.

18. A method as claimed in any one of the preceding Claims, wherein the weight ratio of said N-acylated amino acid to said antibiotic is from 1:1 to 4:1.

19. A method according to any one of the preceding Claims, which comprises: solubilizing said N-acylated amino acid in water; adding and dissolving said antibiotic in the resulting; and optionally lyophilizing the solution to provide a powdery mixture.

20. A method according to Claim 19, in which said N-acylated amino acid is solubilized by dispersing it in water and adding sufficient of a base to adjust the pH to a value of from 5.5 to 9.

21. The use for the manufacture of a medicament for the treatment of bacterial infections of:

(a) a penem or carbapenem antibiotic;

in association with:

(b) a pharmaceutically acceptable N-acylated derivative of an amino acid wherein the amino group and the carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof, provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.

22. The use as claimed in Claim 21, wherein said N-acylated amino acid is:
N-(p-toluoyl)-β-alanine
N-(4-methoxybenzoyl)-β-alanine
N-(3-hydroxy-2-naphthoyl)-β-alanine
N-benzoylglycyl-β-alanine
N-benzoyl-β-alanine
N-benzoyl-5-aminovaleric acid
N -benzoyl-6-aminohexanoic acid
N-cyclohexanecarbonyl-6-aminohexanoic acid
N-(N -methylnicotinoyl)-6-aminohexanoic acid
N-benzoyl-8-aminooctanoic acid
N-benzoylalanine
N-(1-naphthoyl)alanine

N-benzoylvalylalanine
N-benzoyl-2-aminobutyric acid
N-benzoylnorvaline
N-valerylvaline
N-benzoylalanylvaline
N-benzoylvaline
N-benzoylleucine
N-benzoylglycylphenylalanylleucine
N-benzoylnorleucine
N-benzoylglycylphenylalanine
N-benzoylalanylphenylalanine
N-cyclohexanecarbonylleucylphenylalanine
N-benzoyl-O-methyltyrosine
N-benzoylmethionine
N-phenylacetylmethionine
N-benzoylvalylmethionine
N-benzoylethionine
N-(4-methoxybenzyloxycarbonyl)ethionine
N-benzoylthreonine
N-benzoylhistidine
N-(p -toluoyl)histidine
N-(4-methoxybenzoyl)histidine
N-(4-methoxybenzoyl)-3-aminobutyric acid
or
N-butuyryl-3-amino-3-phenylpropionic acid.

23. The use as claimed in Claim 21 or Claim 22, wherein said antibiotic is:
(5R,6S)-2-{2-[(aminomethylene)amino]ethylthio}-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S)-methyl-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3S-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(R)-methyl-2-carbapenem-3-carboxylic acid
(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S-methyl-2-carbapenem-3-carboxylic acid
or
(5R,6S)-2-[(3S)-1-acetimidoyl-5(S)-carbamoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 86 30 8321

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP-A-0 048 301 (MERCK) * Page 3; claims *	1,2,14	A 61 K 31/40 A 61 K 31/43 // (A 61 K 31/40 A 61 K 31:195)
A	EP-A-0 091 594 (SANRAKU-OCEAN CO.) * Claims *	1,2,14	(A 61 K 31/43 A 61 K 31:195)
P,A D	EP-A-0 178 911 (SANKYO) * Claims *	1-24	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K 31/00
C 07 D 487/00
C 07 D 499/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	14-01-1987	CHOULY J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503 03.82